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ORGANIC SYNTHESSES

AN ANNUAL PUBLICATION OF SATISFACTORY
METHODS FOR THE PREPARATION
OF ORGANIC CHEMICALS

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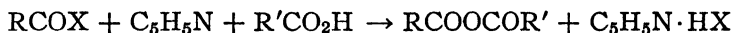
NOMENCLATURE

Preparations are listed under the names which are used commonly for the compounds. For the convenience of those who wish to make a complete survey of the literature on any preparation, the *Chemical Abstracts* **indexing name** for each compound is given as a subtitle when that name differs from the title of the preparation.

NOTICE TO SUBMITTERS OF PREPARATIONS

Organic Syntheses invites the submission of preparations of compounds which are of general interest or which illustrate useful synthetic methods. Preparations are welcomed particularly from those who have had occasion to work out the optimum conditions of preparation. The directions should be written in the style employed in the latest volume of *Organic Syntheses*. A copy of the current style sheet will be sent to those who request it. Full details for all steps in the procedures should be included, and the range of yields should be reported rather than the maximum yield obtainable. Wherever possible the melting point, the boiling range at various pressures, and the refractive index of each product should be given. The method of preparation or source of compounds used should be recorded as well as criteria of purity. Two copies of the directions should be sent to the Secretary. Additions, corrections, and improvements to previously published preparations are likewise welcomed.

ACID ANHYDRIDES



Submitted by C. F. H. ALLEN, C. J. KIBLER, D. M. McLACHLIN, and
C. V. WILSON.

Checked by CLIFF S. HAMILTON, DEXTER SHARP, and R. KRETZINGER.

1. Procedure

A. *Heptioic anhydride (enanthic anhydride)*. In a 250-ml. round-bottomed three-necked flask, equipped with a stirrer, dropping funnel, and thermometer, are placed 15.8 g. (16.1 ml., 0.2 mole) of dry pyridine (Note 1) and 25 ml. of dry benzene (Note 2). Then 14.8 g. (15.5 ml., 0.1 mole) of heptoyl chloride (Note 3) is added rapidly to the stirred solution. The temperature rises only slightly, and a pyridinium complex separates. While stirring is continued, 13.0 g. (14.1 ml., 0.1 mole) of heptioic acid (Note 3) is added from the dropping funnel over a period of 5 minutes. The temperature rises rapidly to 60–65° (Note 4), and pyridine hydrochloride is formed. After stirring for 10 minutes, the solid is collected on a chilled Büchner funnel and washed twice with 25-ml. portions of dry benzene (Note 5).

The filtrate is concentrated under reduced pressure on the steam bath, and the residue is distilled using a 200-ml. modified Claisen flask.¹ The fraction boiling up to 155°/12 mm. is discarded; the anhydride is collected at 155–162°/12 mm. (170–173°/15 mm.). It amounts to 19–20 g. (78–83%).

B. *p-Chlorobenzoic anhydride (benzoic anhydride, p,p'-dichloro-)*. A mixture of 17.5 g. (0.1 mole) of *p*-chlorobenzoyl chloride (Note 6) and 50 ml. (0.6 mole) of pyridine in a loosely stoppered 200-ml. flask is warmed on the steam bath for 5 min-

utes and poured upon 100 g. of cracked ice and 50 ml. of concentrated hydrochloric acid (sp. gr. 1.18). The anhydride separates at once; as soon as the ice has melted sufficiently the mixture is filtered by suction. The solid is washed once with 15 ml. of methanol, then with 15 ml. of dry benzene. The yield is 14.2–14.6 g. (96–98%). Though suitable for most purposes, the crude product can be purified by recrystallization from 250 ml. of dry benzene; the recovery is 90%; it melts at 192–193°.

2. Notes

1. The pyridine was Eastman grade which was dried by long standing over potassium hydroxide for A but used without further drying in B. Presumably the anhydride would not be obtained in good yield¹¹ from pure acid chloride in B, if the reaction mixture did not contain about 0.9 g. of water.

2. The benzene is dried by distilling the first 10% and using the residue directly.

3. The heptoyl chloride, b.p. 173–175°, and the heptonic acid, b.p. 108–109°/9 mm., were obtained from the Eastman Kodak Company.

4. When preparing larger amounts, it would probably be better to control the temperature by external cooling as well as by the rate of addition of the acid.

5. Pyridine hydrochloride is hygroscopic; the filtration should be done rapidly, using a Büchner funnel.

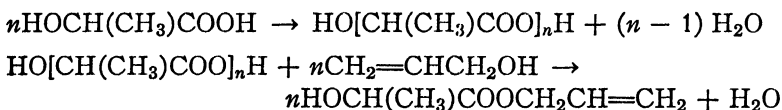
6. *p*-Chlorobenzoyl chloride (m.p. 14–15°) is readily obtained by refluxing and stirring 156 g. (1.0 mole) of *p*-chlorobenzoic acid (obtained by the procedure for the *o*-isomer²) and 200 g. (1.7 moles) of thionyl chloride until solution is complete. The unused thionyl chloride is distilled, under slightly reduced pressure, and the product at 10 to 25 mm.; the yield of *p*-chlorobenzoyl chloride, b.p. 119–120°/22 mm. is 131–142 g. (75–81%). An additional amount can be secured by working up the fore-run and residue.

3. Methods of Preparation

The procedures as outlined are applicable to both the aliphatic and aromatic series. They are superior to the common interchange method³ in that they avoid the fractional distillation which is very troublesome in the aliphatic series. They have been used in numerous instances⁴⁻¹² and can be adapted to give mixed anhydrides.¹³ Benzoic anhydride has been obtained, by closely related procedures, from benzoic acid and benzoyl chloride by heating under reduced pressure¹⁴ or in the presence of zinc chloride.¹⁵

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ALLYL LACTATE**(Lactic acid, allyl ester)**

Submitted by CHESSE E. REHBERG.

Checked by H. R. SNYDER and FRED E. BOETTNER.

1. Procedure

Six hundred and seventy-five grams (6 moles) of 80% lactic acid (Note 1), 300 ml. of benzene and 5 ml. of concentrated sulfuric acid are placed in a 3-l. three-necked round-bottomed flask having a capillary ebullition tube in one neck. The flask is attached to a Vigreux column 75 cm. in length, having at its top a trap of the Dean and Stark type, preferably the Barrett modification carrying a stopcock (Note 2), and a reflux condenser. The mixture is refluxed, and the aqueous layer is withdrawn from the trap until liberation of water becomes slow or until noticeable darkening of the material begins (Note 3). Then 1394 g. (1635 ml. or 24 moles) of allyl alcohol is added (Note 4), and refluxing and removal of water are continued until production of water ceases (Note 5). The acid catalyst is then neutralized with anhydrous sodium acetate (18 g.) (Note 6), and the fractionating column is replaced by a short distillation head leading to a 3-l. round-bottomed receiving flask cooled in salt and ice. The liquid is distilled rapidly under diminished pressure, first at the water pump and finally at a pressure of about 5 mm. A viscous residue (about 130 g.) containing inorganic salts is discarded. The distillate is fractionated through the column used in the first steps. The trap at the reflux condenser is replaced with a still head arranged for controlled partial take-off. The first fraction is the benzene-allyl alcohol binary azeotrope, which distils at 76.8°

and contains 17.4% of the alcohol. Frequently a small amount of allyl ether is obtained at 94–95°. Allyl alcohol is then distilled at 97° until most of it is removed and the temperature of the residue in the pot reaches about 120°. The pressure is reduced to about 50 mm. while the remainder of the alcohol is removed. Finally the allyl lactate is distilled at 56–60°/8 mm. (Note 7). It amounts to 693–710 g. (89–91%) (Note 8).

2. Notes

1. The lactic acid used was the commercial edible grade and was almost colorless. The checkers used 635.6 g. of 85% lactic acid, U.S.P. The lower grades of commercial acid probably would give somewhat lower yields.

2. A suitable piece of apparatus is listed in Catalog LP-24, p. 43 (1944), of the Corning Glass Works.

3. Generally, about 35 ml. of water per mole of 80% lactic acid is obtained at this stage, and 4–6 hours of refluxing is required for its removal. The linear lactic acid polymer thus produced contains approximately 3 lactic acid units.

4. A large excess of alcohol is essential for a high yield of ester. Thus, when the ratio of alcohol to acid is 4:1, the yield is 90%; when it is 3:1, the yield is 85–88%; when it is 2:1, the yield is about 65%; and when it is 5:3, the yield is 58–60%.

5. The checkers found this distillation to require about 16 hours. The distillate is the ternary azeotrope. It consists of 8.6% water,¹ 9.2% allyl alcohol, and 82.2% benzene, and boils at 68.2°. The aqueous layer contains some allyl alcohol, though this loss is insignificant, since only about 15 ml. of the aqueous layer is obtained from each mole of lactic acid used.

6. It is essential to neutralize any strong acid present before distilling lactic esters; otherwise, condensation by ester interchange occurs, with liberation of alcohol and production of "polylactic acid," a linear polyester. Other neutralizing agents, such as alkali or alkaline-earth hydroxides or carbonates, doubtless could be used satisfactorily instead of sodium acetate.

7. Allyl lactate is a clear, colorless, mobile liquid boiling at

60°/8 mm., 79°/25 mm., and 175–176°/740 mm. Other properties are d_4^{20} , 1.0452; n_D^{20} , 1.4369.

8. This method of preparation is suitable for producing primary alkyl lactates but is unsatisfactory for β -methallyl lactate because the strong mineral acid catalyzes the rearrangement of methallyl alcohol to isobutyraldehyde. Methyl lactate² can be made conveniently (80–85% yield) by heating 1 mole of lactic acid condensation polymer with 2.5–5 moles of methanol and a small quantity of sulfuric acid at 100° for 1–4 hours in a heavy-walled bottle, such as is used for catalytic hydrogenation with a platinum catalyst.

3. Methods of Preparation

Allyl lactate has been prepared by the repeated treatment of lactic acid or its polymer with allyl alcohol in the presence of mineral acid.³

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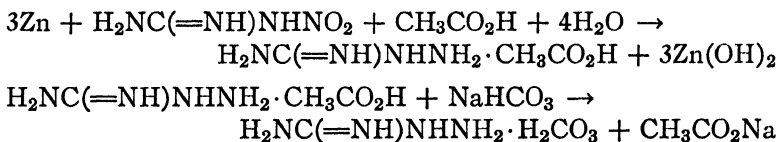
¹ Lange, "Handbook of Chemistry," 4th ed., p. 1217, Handbook Publishers, Sandusky, Ohio, 1941.

² Filachione, Fein, Fisher, and Smith, "Continuous Methods for Dehydrating Lactic Acid and Preparing Methyl Lactate and Methyl Acetoxypropionates," presented before the Division of Industrial and Engineering Chemistry at the 105th meeting of the American Chemical Society, Detroit, Michigan, April 12, 1943.

³ Fisher, Rehberg, and Smith, *J. Am. Chem. Soc.*, **65**, 763–767 (1945).

AMINO GUANIDINE BICARBONATE

(Guanidine, amino-, bicarbonate)



Submitted by R. L. SHRINER and FRED W. NEUMANN.

Checked by HOMER ADKINS and M. J. CURRY.

1. Procedure

Two hundred and sixteen grams (2.07 moles) of nitroguanidine¹ and 740 g. (11.3 moles) of purified zinc dust (Note 1) are thoroughly ground together in a mortar, and then enough water (about 400 ml.) is added with stirring with the pestle to form a thick paste. The paste is transferred to a 3-l. enameled can or beaker surrounded by an ice bath. A solution of 128 g. (2.14 moles) of glacial acetic acid in 130 ml. of water is cooled to 5° in another 3-l. beaker, which is fitted with a strong mechanical stirrer and surrounded by an ice bath. The paste of nitroguanidine and zinc dust, cooled to 5°, is added slowly with mechanical stirring, keeping the temperature of the reaction mixture between 5° and 15°. A total of about 1 kg. of cracked ice is added to the mixture from time to time as the mixture becomes too warm or too thick to stir. The addition of the paste takes about 8 hours, and the final volume of the mixture is about 1.5 l. (Note 2). The mixture is then slowly warmed to 40° on a water bath with continued stirring, and this temperature is maintained for 1–5 minutes, until reduction is complete (Note 3).

The solution is immediately separated from the insoluble material by filtration on a 20-cm. Büchner funnel, and the cake is sucked as dry as possible. The residue is transferred to the 3-l. beaker, triturated well with 1 l. of water, and then separated from the liquid by filtration. In the same manner, the residue

is washed twice more with two 600-ml. portions of water. The filtrates are combined and placed in a 5-l. round-bottomed flask. Two hundred grams of ammonium chloride is added, and the solution is mechanically stirred until solution is complete (Note 4). Stirring is continued, and 220 g. (2.62 moles) of solid sodium bicarbonate is added during a period of about 10 minutes. The aminoguanidine bicarbonate begins to precipitate after a few minutes, and the solution is then placed in a refrigerator overnight. The precipitate is collected by filtration on a Büchner funnel. The cake is removed to a 1-l. beaker and mixed with a 400-ml. portion of a 5% solution of ammonium chloride and filtered. It is again washed with two 400-ml. portions of distilled water, the wash solution being removed each time by filtration. Finally the solid is pressed down on the Büchner funnel; the mat is broken up with a spatula and washed while on the funnel with two 400-ml. portions of 95% ethanol and then with one 400-ml. portion of ether. After air drying, the aminoguanidine bicarbonate amounts to 180–182 g. (63–64%) of a white solid, melting at 172° with decomposition (Notes 5 and 6).

2. Notes

1. The zinc is purified by stirring 1.2 kg. of commercial zinc dust with 3 l. of 2% hydrochloric acid for 1 minute. The acid is removed by filtration, and the zinc is washed in a 4-l. beaker with one 3-l. portion of 2% hydrochloric acid, three 3-l. portions of distilled water, two 2-l. portions of 95% ethanol, and finally with one 2-l. portion of absolute ether, the wash solutions being removed each time by filtration. Then the material is thoroughly dried and any lumps are broken up in a mortar.

2. The solution becomes basic to litmus after one-half to three-fourths of the paste has been added. Lower yields are obtained if a larger excess of acetic acid is employed.

3. The state of reduction can be determined by placing 3 drops of the reaction mixture in a test tube containing 5 ml. of a 10% solution of sodium hydroxide and then adding 5 ml. of a freshly prepared saturated solution of ferrous ammonium sul-

fate. A red coloration indicates incomplete reduction; when the reduction is complete, only a greenish precipitate is observed. The mixture should not be heated after this test shows that reduction is complete.

4. The presence of the ammonium chloride prevents the coprecipitation of zinc salts when sodium bicarbonate is added to the solution to precipitate the aminoguanidine as the bicarbonate. If the solution is not clear at this step, it should be filtered.

5. The aminoguanidine bicarbonate is pure enough for most purposes. It should not be recrystallized from hot water, since decomposition will occur.

6. W. W. Hartman and Ross Philips have submitted a procedure suitable for the preparation of aminoguanidine bicarbonate on a larger scale. The sulfates of methylisothiurea and of hydrazine are allowed to react with the evolution of methyl mercaptan. In a 30-gal. crock are placed 10 l. of water and 5760 g. (20 moles) of methylisothiurea sulfate.⁴ In a 22-l. flask, 5200 g. (40 moles) of hydrazine sulfate⁵ is stirred with 12 l. of water, and 40% sodium hydroxide is added until all the hydrazine sulfate has dissolved and the solution is just neutral to Congo paper. The exact amount of alkali is noted and a duplicate amount added. The hydrazine solution is then added to the 30-gal. crock with stirring, as fast as possible, without allowing the foam to overflow the crock. The mixing is done out-of-doors, or in an efficient hood, since large volumes of methyl mercaptan are evolved. If the reaction is carried out on a smaller scale in 12- or 22-l. flasks, using appropriate amounts of material, the methyl mercaptan evolved may be absorbed in cold sodium hydroxide solution and isolated if desired. The solution is stirred until evolution of mercaptan stops, and then a few liters of water are distilled off under reduced pressure to free the solution entirely from mercaptan. The residual liquor is chilled in a crock, and a crop of hydrated sodium sulfate is filtered off, washed with ice water, and discarded. The filtrate is warmed to 20–25°, 25 ml. of glacial acetic acid is added, then 4 kg. of sodium bicarbonate, and the solution is stirred vigorously for 5 minutes and thereafter occasionally during an hour, or until the precipitate no longer in-

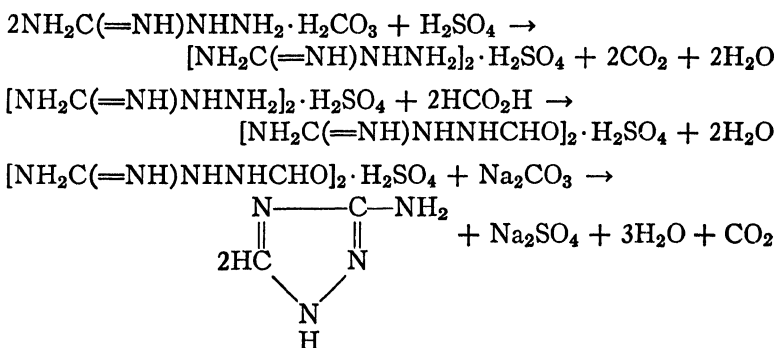
creases. The precipitate is filtered with suction and washed with ice water and then with methyl alcohol, and is dried at a temperature not above 60–70°. The yield is 3760 g. (69% of the theoretical amount). Hydrazine sulfate may be recovered from the final filtrate, if the filtrate is strongly acidified with sulfuric acid and allowed to cool.

3. Methods of Preparation

Numerous references for the preparation of aminoguanidine bicarbonate and other salts can be found in the excellent review article, "The Chemistry of Aminoguanidine and Related Substances" by Lieber and Smith.² More recently, it has been prepared by treating a cyanamide solution at 20–50° with hydrazine and carbon dioxide.³

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3-AMINO-1,2,4-TRIAZOLE**(1,2,4-Triazole, 3-amino-)**

Submitted by C. F. H. ALLEN and A. BELL.

Checked by R. L. SHRINER and FRED W. NEUMANN.

1. Procedure

To 68 g. (0.5 mole) of aminoguanidine bicarbonate (p. 7) in a 500-ml. round-bottomed flask is added carefully the cold dilute sulfuric acid (0.24 mole), made from 24.5 g. of concentrated acid (sp. gr. 1.84) and 50 ml. of water. After the gas evolution has subsided, the solution is heated for 1 hour on a steam bath and then evaporated to dryness under a pressure of about 15 mm.

To the white residue (Note 1) are added 25 g. of 98–100% formic acid and 2–3 drops of concentrated nitric acid. The mixture is heated for 24 hours on a steam bath. The resulting syrup is dissolved in 100 ml. of water and, with the temperature at 50°, is carefully treated with 25 g. of anhydrous sodium carbonate. The solution is then placed in an evaporating dish and evaporated to dryness on the steam bath. The residue is extracted twice by boiling it with 200-ml. portions of absolute ethanol, and the alcohol solutions are filtered. The alcohol is removed by evaporation and the residue triturated with 100 ml. of a mixture of equal

parts of dry ethanol and dry ether and collected on a filter. The yield of crude 3-amino-1,2,4-triazole is 33–36 g. (79–86%). The melting point varies (Note 2). The crude product is purified by dissolving it in 140 ml. of boiling absolute ethanol, treating it with 1 g. of Norite, and filtering. To the filtrate is added 50 ml. of ether, and the solution is placed in a refrigerator for 48 hours. The aminotriazole crystallizes and is collected by filtration. It weighs 20–25 g. (60–73% recovery) and melts at 153° after softening at 148°.

2. Notes

1. If aminoguanidine sulfate is available, the first part of this preparation may be omitted and 61.5 g. of the sulfate treated with formic acid as directed in the second paragraph.

2. The crude material from one run melted at 125–143°, but the melting point changed to 140–150° upon drying over phosphorus pentoxide at 100° under a pressure of 10 mm. Another crude sample melted at 145–147°.

3. Methods of Preparation

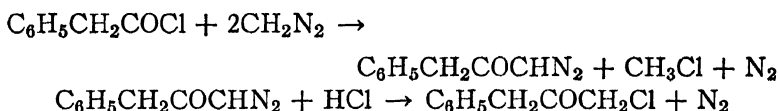
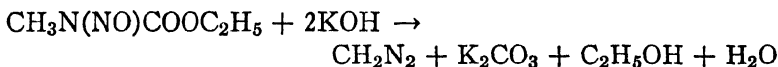
3-Amino-1,2,4-triazole has been prepared by evaporating formylguanidine nitrate with sodium carbonate,¹ and from 5(3)-amino-1,2,4-triazole carboxylic acid-3(5) by heating above its melting point,^{2,3,4} or by a long digestion with acetic acid.¹

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BENZYL CHLOROMETHYL KETONE

(2-Propanone, 1-chloro-3-phenyl-)



Submitted by WARREN D. MCPHEE and ERWIN KLINGSBERG.

Checked by NATHAN L. DRAKE and MARVIN SCHWARTZ.

1. Procedure

Diazomethane is poisonous and explosive.

Twelve grams (0.21 mole) of ground potassium hydroxide is dissolved in 45 ml. of *n*-propyl alcohol in a three-necked 500-ml. flask set on a steam bath so that the mixture can be warmed. Two necks of the flask are fitted with dropping funnels. A Vigreux fractionating column (25 cm. in length and 12 mm. in diameter) is inserted in the third neck of the flask. The column is connected, through a condenser and adapter, to a filter flask set in ice as the receiver. The side arm of the receiver is fitted with a drying tube. About an hour and a half is required to dissolve the hydroxide, whereupon an additional amount of alcohol is added to bring the total volume to 50 ml. The solution is then cooled, and 100 ml. of absolute ether is added. Through one dropping funnel is added dropwise 20 ml. of nitrosomethylurethan¹ (equivalent to 0.10 mole of diazomethane; Note 1). The flask is warmed on a steam bath so that diazomethane distils over with ether while the nitrosomethylurethan is being added. The addition requires about 20 minutes. During this operation more dry ether is added as needed, through the second dropping funnel, until the total volume of ether distillate is 250 ml. When the

ether distilling over is colorless, the distillate is transferred to another three-necked 500-ml. flask, equipped with a mechanical stirrer, a dropping funnel, and a condenser. To the stirred solution is added, over a period of 15 minutes, a solution of 6.6 ml. (7.7 g., 0.050 mole) of phenylacetyl chloride in 10 ml. of absolute ether. A copious evolution of nitrogen accompanies this operation.

After standing for 2 hours, the solution of diazoketone is cooled in ice and treated with dry gaseous hydrogen chloride until the passage of the gas no longer causes evolution of nitrogen (Note 2). At the end of this time, the original yellow color of the solution has changed to an orange-red. About 100 ml. of water is slowly and cautiously added to the ether solution in order to cause a separation into two layers. An additional 50 ml. of water is then added to give a more complete separation. The ether layer is then washed with two 50-ml. portions of a 5% solution of sodium carbonate in water. The ether solution is dried with anhydrous calcium chloride or calcium sulfate, the solvent evaporated, and the product distilled. The yield of benzyl chloromethyl ketone, b.p. 133–135°/19 mm. or 96–98°/1 mm., is 7.0–7.1 g. (83–85%) (Notes 3 and 4).

2. Notes

1. The yield of diazomethane from nitrosomethylurethan is usually given as 0.005 mole per ml.² Another method for the preparation of diazomethane has recently been described.³

2. This usually requires about 25 minutes. In certain runs, the hydrogen chloride caused the deposition of a dark red flocculent solid, which was removed by filtration. The yield was then 5–10% lower. This can apparently be avoided by waiting 2 hours, as directed, and by cooling the solution before the hydrogen chloride treatment.

3. This method is general for chloromethyl ketones. Yields of 75–85% may be obtained using hydrocinnamoyl chloride or diphenylacetyl chloride.

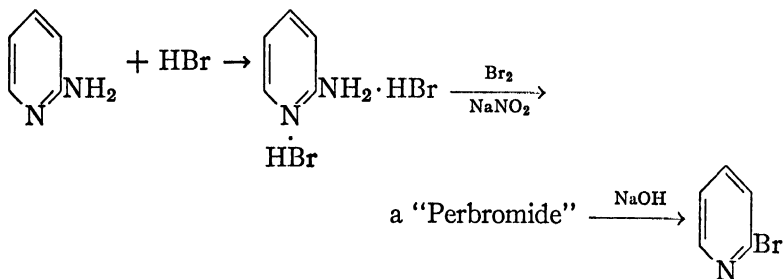
4. *Diazomethane is poisonous and explosive.⁴ The preparation should be carried out in a good hood.*

3. Method of Preparation

Benzyl chloromethyl ketone has been prepared by the reaction of diazomethane with phenylacetyl chloride. The method of Clibbens and Nierenstein,⁵ in which one equivalent of diazomethane is added to the acyl chloride and the chloromethyl ketone obtained directly, could not be duplicated by Bradley and Schwarzenbach⁶ or by the submitters.

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2-BROMOPYRIDINE**(Pyridine, 2-bromo-)**

Submitted by C. F. H. ALLEN and JOHN R. THIRTLE.
 Checked by CLIFF S. HAMILTON and CAROL K. IKEDA.

1. Procedure

In a 5-l. 3-necked flask fitted with a mechanical stirrer (Note 1), a dropping funnel, and a thermometer for reading low temperatures is placed 790 ml. (7 moles) of 48% hydrobromic acid. The flask and contents are cooled to 10–20° in an ice-salt bath, and 150 g. (1.59 moles) of 2-aminopyridine (Note 2) is added over a period of about 10 minutes. While the temperature is kept at 0° or lower, 240 ml. (4.7 moles) of bromine is added dropwise (Note 3). A solution of 275 g. (4 moles) of sodium nitrite in 400 ml. of water is added dropwise over a period of 2 hours, the temperature being carefully maintained at 0° or lower (Note 4). After an additional 30 minutes of stirring, a solution of 600 g. (15 moles) of sodium hydroxide in 600 ml. of water is added at such a rate that the temperature does not rise above 20–25° (Note 5). The nearly colorless reaction mixture is extracted with

four 250-ml. portions of ether (Note 6). The extract is dried for 1 hour over 100 g. of solid potassium hydroxide and is then distilled through a Vigreux column 15 cm. in length. 2-Bromopyridine distils at 74–75°/13 mm., and the yield is 216–230 g. (86–92%) (Note 7).

2. Notes

1. A stirrer which gives efficient stirring near the walls of the flask is advisable. The fittings should not be gas tight since oxides of nitrogen and bromine are evolved during the reaction. It is advisable to work in a hood or out-of-doors.

2. The checkers used Eastman Kodak Company's Practical grade of 2-aminopyridine.

3. The reaction mixture thickens, owing to formation of a yellow-orange perbromide during the addition of about one-half of the bromine; the first half of the bromine is added over a period of 30 minutes; the second half, over a period of 15 minutes.

4. The ice-salt bath is renewed before the sodium nitrite is added and once during the addition.

5. The color of the reaction mixture darkens during the addition of the alkali but becomes light yellow toward the end.

6. The separation into layers may not take place readily. The use of a "lilly" may be helpful in separating the ether layer. A "lilly" is essentially a U-tube having unequal legs, the shorter of which has a flared top. It is easily prepared from a thistle or funnel tube by making a U bend just below the funnel. In use, a suction flask to act as a receiver is attached by means of rubber tubing. With this device it is a simple matter to draw off the upper layer when making separations, in any wide-mouth bottle or open jar. It may be necessary to filter the intermediate layer before attempting the separation.

7. This procedure can be used with 7 times the above amounts in a 22-l. flask, cooled in a half-barrel. A "Lightnin" stirrer is required (Model C-2).

3. Methods of Preparation

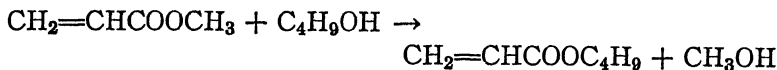
2-Bromopyridine has been made by direct bromination of pyridine;² from N-methyl-2-pyridone with phosphorus pentabromide and phosphorus oxybromide;³ from 2-aminopyridine by diazotization with amyl nitrite in 20% hydrobromic acid;⁴ from sodium 2-pyridinediazotate by solution in concentrated hydrobromic acid;⁵ and from 2-aminopyridine by diazotization in the presence of bromine and concentrated hydrobromic acid.⁶ The method described here is essentially that of Craig.

References

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² Wibaut and Den Hertog, *Rec. trav. chim.*, **51**, 385 (1932); McElvain and Goese, *J. Am. Chem. Soc.*, **65**, 2230 (1943).
³ Fischer, *Ber.*, **32**, 1303 (1899).
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⁵ Tschitschibabin and Tjashelowa, *J. Russ. Phys. Chem. Soc.*, **50**, 495 (1918) [*Chem. Zentr.*, **1923** III, 1021].
⁶ Craig, *J. Am. Chem. Soc.*, **56**, 232 (1934).

n-BUTYL ACRYLATE

(Acrylic acid, *n*-butyl ester)



Submitted by CHESSIE E. REHBERG.

Checked by H. R. SNYDER and FRED E. BOETTNER.

1. Procedure

In a 2-l. two-necked round-bottomed flask having a capillary ebullator tube in one neck (Note 1) are placed 371 g. (5 moles)

of *n*-butyl alcohol, 861 g. (10 moles) of methyl acrylate, 20 g. of hydroquinone, and 10 g. of *p*-toluenesulfonic acid (Note 2). The flask is attached to an all-glass fractionating column, preferably one without packing such as the Vigreux type (Note 3), and the solution is heated to boiling in an oil bath. The column is operated under total reflux until the temperature of the vapors at the still head falls to 62–63°, which is the boiling point of the methanol-methyl acrylate azeotrope (Note 4). This azeotrope is then distilled as rapidly as it is formed, the temperature at the still head not being allowed to exceed 65°. When the production of methanol has become very slow (6–10 hours), the excess methyl acrylate is distilled, and the butyl acrylate is then distilled, preferably at 10–20 mm. It boils at 39°/10 mm., 84–86°/101–102 mm., and at about 145° at atmospheric pressure. The yield is 500 to 600 g. (78–94%) (Note 5).

2. Notes

1. The capillary is used to introduce a gas to prevent bumping and superheating during the vacuum distillation of the product. As air has some tendency to catalyze polymerization of the acrylic ester, if it is introduced through the capillary the amount must be as small as possible. The gas introduced should be an inert one, such as carbon dioxide or nitrogen. If polymerization is troublesome, it may be advantageous to pass in a slow stream of carbon dioxide through the capillary during the entire reaction period.

2. Sulfuric acid is also a very satisfactory catalyst; aluminum alkoxides also are useful, especially when the alcohols would be adversely affected by strong acids. Sodium alkoxides produce undesirable side reactions and give lower yields. When alkaline catalysts are employed, an alkaline polymerization inhibitor, such as *p*-phenylenediamine or phenyl- β -naphthylamine, should be used instead of hydroquinone.

3. The fractionating column should be one which can be cleaned readily if a polymer is formed in it. A large number of plates is not required, though the column should be capable of separating the methanol-methyl acrylate azeotrope (b.p. 62–63°) from methyl acrylate (b.p. 80°) and butanol (b.p. 117°) from butyl acrylate (b.p. 145°). The necessity of effecting the latter separation can be practically eliminated by allowing the reaction to go virtually to completion, all the butanol thus being consumed. This can be done by extending the reaction period as long as reaction occurs and by adding a considerable excess of methyl acrylate. Instead of the twofold excess specified, three or four times the theoretical amount may be used with benefit. The larger amount is especially desirable when the acrylate of a relatively unreactive alcohol is being prepared.

4. The methanol-methyl acrylate azeotrope contains about 45% methyl acrylate, which can be recovered by washing out the methanol with a large volume of water or brine; the acrylate is purified by drying and distilling. An inhibitor, such as hydroquinone, should always be added to any acrylic ester before attempting to distil it, and, unless it is stored in a refrigerator, the distilled ester should not be kept more than a few hours without the addition of a small amount (0.1–1.0%) of an inhibitor.

5. Yields of the primary alkyl acrylates vary somewhat, owing to occasional losses through formation of polymer, but are usually in the range of 85–99%. Some secondary alcohols react very slowly, others readily. The method has been applied to more than fifty alcohols, some of which (with percentage yields) are listed below: ethyl, 99%; isopropyl, 37%; *n*-amyl, 87%; isoamyl, 95%; *n*-hexyl, 99%; 4-methyl-2-pentyl, 95%; 2-ethylhexyl, 95%; capryl, 80%; lauryl, 92%; myristyl, 90%; allyl, 70%; furfuryl, 86%; citronellyl, 91%; cyclohexyl, 93%; benzyl, 81%; β -ethoxyethyl, 99%; β -(β -phenoxyethoxy)ethyl (from diethylene glycol monophenyl ether), 88%.

3. Methods of Preparation

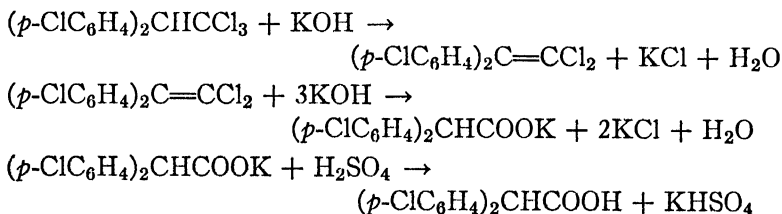
n-Butyl acrylate has been prepared by direct esterification,¹ by debromination of *n*-butyl α,β -dibromopropionate with zinc,² by treatment of either butyl β -chloropropionate¹ or butyl β -bromopropionate¹ with diethylaniline, and by the pyrolysis of butyl β -acetoxypionate.³ Direct esterification and alcoholysis of methyl or ethyl acrylate have been recommended for the preparation of the higher alkyl acrylates.⁴

References

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- ⁴ Neher, *Ind. Eng. Chem.*, **28**, 267 (1936).

DI-(*p*-CHLOROPHENYL)-ACETIC ACID

(Acetic acid, di-(*p*-chlorophenyl))



Submitted by OLIVER GRUMMITT, ALLEN BUCK, and RICHARD EGAN.

Checked by LEE IRVIN SMITH, R. T. ARNOLD, and PAUL N. CRAIG.

1. Procedure

A mixture of 400 ml. of diethylene glycol (Note 1) and 49.5 g. (0.14 mole) of 1,1-di-(*p*-chlorophenyl)-2,2,2-trichloroethane

(Note 2) is placed in a 1-l. three-necked flask fitted with a stirrer, reflux condenser, and thermometer. To this is added a solution of 63 g. (1.12 mole) of potassium hydroxide in 35 ml. of water. The mixture is stirred and refluxed for 6 hours at such a rate that the temperature is maintained at 134–137° (Notes 3 and 4). The mixture is allowed to cool and, with vigorous stirring, is poured into 1 l. of cold water. The insoluble material is filtered and washed twice with 50-ml. portions of warm water (Note 5). The filtrate is then boiled gently for 5 minutes with 2 g. of Norite; the carbon is removed, the filtrate is acidified to litmus with 20% sulfuric acid (approximately 120 ml.), and then an additional 30 ml. of acid is added. The mixture is cooled to 0–5°; the precipitate is collected by filtration under suction, washed free of sulfate ions with water, and dried at 100–110°. The product is di-(*p*-chlorophenyl)-acetic acid melting at 163–165°; it weighs 27–28.5 g. (69–73%). For purification, this material is dissolved in 100 ml. of boiling 95% alcohol, the solution is filtered, and approximately 45 ml. of water is added to the boiling filtrate until it just becomes turbid. The solution is then cooled to 0–5°, and the solid is removed by suction filtration. The material weighs 25–26 g. and melts at 164–166°.

2. Notes

1. Diethylene glycol with a boiling range of 230–270°, from Carbide and Carbon Chemicals Corporation, is satisfactory.

2. A purified grade of 1,1-di-(*p*-chlorophenyl)-2,2,2-trichloroethane (DDT) melting at 105–106° should be used. It can be obtained by crystallizing the technical material from alcohol. Thus, 100 g. of technical DDT melting at 81–96°, when crystallized from 550 ml. of 95% ethanol, gave about 70 g. of material melting at 105–106°.

3. The intermediate product, 1,1-di-(*p*-chlorophenyl)-2,2-dichloroethylene^{1,2} can be isolated readily. The mixture is gradually (7–8 minutes) heated to reflux temperature and is then refluxed 2 minutes. The mixture is cooled and poured into 1 l. of cold water, and the product is removed by suction filtration,

washed well with water, and dried. The yield of crude product melting at 83–86° is 43.5 g. (97%). This may be purified by crystallization from 200 ml. of 95% ethanol; the product weighs 39.5 g. and melts at 86.5–88°.

4. Longer reaction times or higher temperatures favor the formation of di-(*p*-chlorophenyl)-methane; see Note 5.

5. The insoluble material consists of silica, 1,1-di-(*p*-chlorophenyl)-ethylene and a small amount of di-(*p*-chlorophenyl)-methane³ (melting at 54–55° when purified), formed by decarboxylation of the acid.

3. Methods of Preparation

Di-(*p*-chlorophenyl)-acetic acid has been made by the action of alcoholic potassium hydroxide on 1,1-di-(*p*-chlorophenyl)-2,2-dichloroethane;^{2,4} by the action of barium hydroxide on DDT in ethylene glycol;⁴ and by the condensation of chlorobenzene with glyoxylic acid.⁴

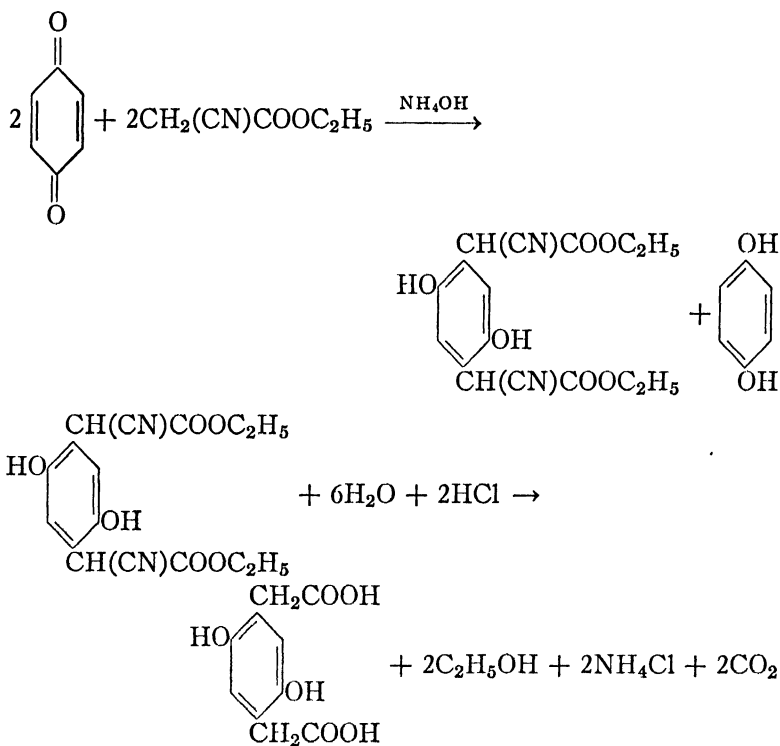
References

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2,5-DIHYDROXY-*p*-BENZENEDIACETIC ACID(*p*-Benzenediacetic acid, 2,5-dihydroxy-)

Submitted by J. II. WOOD and LUCILE COX.

Checked by LEE IRVIN SMITH, SCOTT SEARLES, and R. T. ARNOLD.

1. Procedure

A 3-l. round-bottomed three-necked flask is equipped with a mechanical stirrer, a 500-ml. dropping funnel, and a 250-ml. dropping funnel. The flask is contained in a pneumatic trough through which water at room temperature is circulated. A mix-

ture of 30 ml. of ethyl cyanoacetate and 100 ml. of ethyl alcohol is placed in the flask. Meanwhile 54 g. (0.5 mole) of *p*-benzoquinone in a 1-l. flask is heated to 40° with 500 ml. of 95% ethyl alcohol, and, when practically all the quinone is dissolved, 56 g. (0.5 mole) of ethyl cyanoacetate is added and the mixture is stirred until solution is complete (Note 1). Most of this solution is placed in the 500-ml. dropping funnel, the remainder being added when the funnel becomes sufficiently emptied after the reaction has started.

Twenty-five milliliters of concentrated ammonium hydroxide (Note 2) is introduced into the 3-l. flask. A solution of 100 ml. of concentrated ammonium hydroxide in 150 ml. of water is placed in the 250-ml. dropping funnel, which is loosely stoppered. Stirring is started, and the stopcocks of the two dropping funnels are adjusted so that the solutions will be delivered into the flask at a uniform rate in a period of about 45 minutes (Note 3). Stirring is continued for an additional 10 minutes. The mixture is then permitted to stand for 1 hour, after which the purplish red precipitate is filtered with suction. Any solid material adhering to the walls of the flask is washed onto the funnel with ethyl alcohol. The solid is then washed three times on the funnel with ethyl alcohol (Note 4). The filtrate and washings are discarded. The product is slightly impure diethyl α,α' -dicyano-2,5-dihydroxy-*p*-benzenediacetate and weighs 36–41 g. (43–49%) (Note 5).

For the hydrolysis, 36 g. (0.11 mole) of the residue is transferred to a 1-l. round-bottomed flask equipped with a reflux condenser, and 210 ml. of concentrated hydrochloric acid in 190 ml. of water is added. The mixture is refluxed gently at first, then vigorously (Note 6), until hydrolysis is essentially complete (about 20 hours). Then 180 ml. of water and 4 g. of Norite A are added and the mixture is stirred and boiled for 3 minutes, after which it is rapidly filtered with suction through two layers of hardened filter paper in a Büchner funnel (Note 7). The filtrate, upon cooling to 20° or below, deposits 18 g. (72%) of lightly colored 2,5-dihydroxy-*p*-benzenediacetic acid (Note 8). A snow-

white product is obtained by dissolving 18 g. of this material in 375 ml. of boiling water, treating with 2 g. of Norite A, and filtering. Upon cooling, there is deposited 15 g. (61%) of the acid which melts at 233° (Note 9).

2. Notes

1. Precautions must be taken to prevent ammonia from coming in contact with the quinone before the desired time. The dropping funnel is loosely stoppered, and the flask containing the remainder of the solution is well stoppered.

2. Concentrated ammonium hydroxide (28% NH_3) must be used to obtain a good yield. The ammonium hydroxide may be introduced through either the central opening or the 250-ml. dropping funnel with the precaution given in Note 1.

3. Preferably, all the ammonium hydroxide solution should be added by the time 90% of the quinone solution has been added.

4. This product is insoluble in alcohol, and there is no loss in washing.

5. Slightly lower yields were obtained by the checkers at this point. The yields in three experiments were respectively 32.5, 32.0, and 31.5 g. (39, 38.5, and 38%).

6. In the early stages, considerable foaming usually occurs, and care must be exercised that the foam does not carry part of the insoluble product into the condenser. The insoluble material accumulating on the walls of the flask is occasionally returned to the liquid portion by whirling the flask.

7. Rapid filtration is essential to avoid crystallization in the funnel and to decrease the time the filter paper is in contact with the concentrated acid.

8. The checkers obtained, in two experiments, yields of 71 and 86% of material melting respectively at 232–238° (corr.) and 235–239° (corr.).

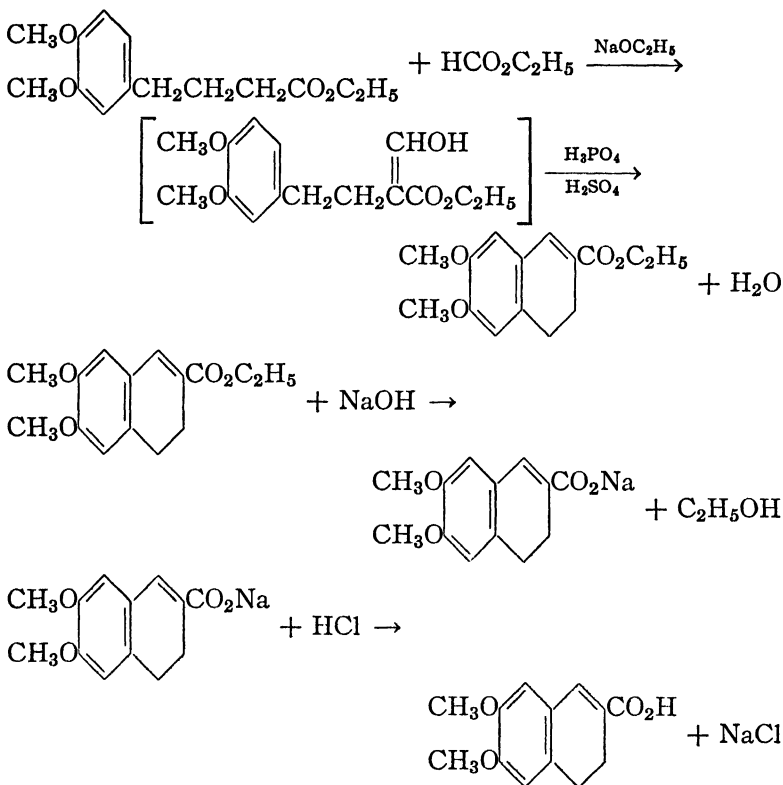
9. The checkers obtained, in two experiments, yields of 63 and 73% at this point. The product was white and melted at 233° (corr.).

3. Methods of Preparation

The method described above is a modification of that described by Wood, Colburn, Cox, and Garland.¹

References

- ¹Wood, Colburn, Cox, and Garland, *J. Am. Chem. Soc.*, **66**, 1540 (1944).

6,7-DIMETHOXY-3,4-DIHYDRO-2-NAPHTHOIC ACID**(2-Naphthoic acid, 3,4-dihydro-6,7-dimethoxy-)**

Submitted by H. L. HOLMES and L. W. TREVOY.

Checked by CLIFF S. HAMILTON and CAROL K. IKEDA.

1. Procedure

A. Ester condensation. A suspension of 9.40 g. (0.41 gram atom) of powdered sodium¹ in 100 ml. of absolute ether is placed in a 1-l. three-necked flask (Note 1) fitted with a reflux condenser, dropping funnel, and a calcium chloride tube. A solution of 23.8 ml. (0.41 mole) of absolute alcohol (Note 2) in 50 ml. of abso-

lute ether is added through the dropping funnel, and the mixture is refluxed on a steam bath for 10–11 hours. The reflux condenser is replaced by a mercury-seal stirrer. A thermometer and a calcium chloride tube are fitted into the third neck of the flask. The suspension of sodium ethoxide in absolute ether is cooled to -10° to -15° in an ice-hydrochloric acid bath, and a solution of 47.85 g. (0.19 mole) of ethyl γ -veratrylbutyrate (Note 3) and 29.6 g. (0.40 mole) of ethyl formate in 100 ml. of absolute ether is added dropwise through the dropping funnel with vigorous stirring (Note 4). The mixture is kept at -10° for 4 hours, and then the thermometer and calcium chloride tube are removed and the stirrer is replaced by a reflux condenser equipped with a calcium chloride tube. The mixture is allowed to come to room temperature and stand for 72 hours. During this time a gas is evolved and a pale yellow solid separates.

On digestion of this solid mass with 1 l. of ice and water, the sodium salt of the enol dissolves in the water, and the unreacted ester is removed by extracting the aqueous layer with two 200-ml. portions of ether (Note 5). The formyl derivative settles out as an oil upon acidification of the aqueous layer with dilute sulfuric acid. The oil is extracted with three 200-ml. portions of ether, and the ethereal extract is washed several times with water and dried over anhydrous sodium sulfate. The ether is distilled, and, to remove traces of ethyl formate, the oil is heated on a steam bath under a pressure of 20–30 mm. for 1 hour. The remaining yellow formyl derivative weighs 27–29 g. (Note 6).

B. Cyclization. The above oil is poured dropwise into a well-stirred mixture of 110 ml. of 90% phosphoric acid (sp. gr. 1.75) and 23.4 ml. of sulfuric acid (sp. gr. 1.83) which is kept at -10° . The temperature is allowed to rise to 0 – 10° , and the stirring is continued for 2 hours. The viscous reaction mixture is poured into 500 ml. of ice and water, and the acid is partially neutralized with 300 ml. of 40% sodium hydroxide solution with efficient cooling. The viscous cream-colored oil is extracted with three 150-ml. portions of ether; the ether extract is washed well with water and sodium bicarbonate solution to remove the last traces of acid and then dried over anhydrous sodium sulfate. The

cyclized ester, after removal of the ether, is a red oil which solidifies upon cooling. The yield is 23–24 g.

C. *Saponification*. The ester is saponified by refluxing for 5 hours with 75 ml. of a 10% sodium hydroxide solution containing 3 ml. of ethyl alcohol; it is then poured into 150 ml. of water and decolorized with Norite. Upon acidification of the alkaline solution with dilute hydrochloric acid, 18–19 g. (40–43%) (Notes 7 and 8) of acid is obtained, melting at 191–193° (corr.).

2. Notes

1. It is suggested that a flask with a ground-glass joint be employed for the condensation as it leads to less discoloration of the formylation product.

2. The absolute ethyl alcohol employed in the condensation was refluxed over calcium oxide for 20 hours and finally distilled from magnesium ethoxide.

3. The ethyl γ -veratrylbutyrate, b.p. 203–207°/20 mm., is obtained in 80% yield by esterification of γ -veratrylbutyric acid by the Fischer-Speier method. The γ -veratrylbutyric acid is prepared by the method of E. L. Martin² from β -(3,4-dimethoxybenzoyl)-propionic acid.

4. The ethereal solution of the two esters should be added at such a rate that the addition is complete in about 1 hour.

5. On distillation, after removal of the ether, 18–20 g. of the ethyl γ -veratrylbutyrate is recovered.

6. The formylation product is too sensitive to purify by distillation even at pressures of 1–2 mm. of mercury.

7. In a similar manner, 3,4-dihydro-2-naphthoic acid, m.p. 111–114° (corr.), and 7-methoxy-3,4-dihydro-2-naphthoic acid, m.p. 149–150.5° (corr.), have been obtained in 35% yields.

8. 6,7-Dimethoxy-3,4-dihydro-2-naphthoic acid can be dehydrogenated³ to give 6,7-dimethoxy-2-naphthoic acid. The yield of the latter was 85% after distillation and crystallization from alcohol.

3. Methods of Preparation

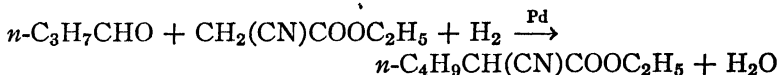
This method of preparation is essentially that used by Robinson and Crowley⁴ for the preparation of 6-methoxy-3,4-dihydro-2-naphthoic acid. They first used concentrated sulfuric acid but found that this reagent caused sulfonation.

References

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²E. L. Martin, *J. Am. Chem. Soc.*, **58**, 1440 (1936); *Org. Syntheses*, **17**, 97 (1937); Coll. Vol. **2**, 499 (1943).
³*Org. Syntheses*, **18**, 59 (1938); Coll. Vol. **2**, 423 (1943).
⁴Robinson and Crowley, *J. Chem. Soc.*, **1938**, 2003.

ETHYL *n*-BUTYLCYANOACETATE

(Caproic acid, α -cyano-, ethyl ester)¹



Submitted by ELLIOT R. ALEXANDER and ARTHUR C. COPE.
Checked by CLIFF S. HAMILTON and ROBERT F. COLES.

1. Procedure

A mixture of ethyl cyanoacetate (Note 1) (56.6 g., 0.5 mole), freshly distilled butyraldehyde (43.2 g., 0.6 mole), 1 g. of palladium on carbon (Note 2), and 80 ml. of glacial acetic acid is placed in a 500-ml. bottle suitable for attachment to a low-pressure reduction apparatus.¹ A solution of piperidine (2.0 ml., 0.02 mole) in 20 ml. of glacial acetic acid is added, and the bottle is connected to the reduction apparatus.

The bottle is alternately evacuated and filled with hydrogen twice, and the mixture is reduced by shaking with hydrogen at 1 to 2 atmospheres (15–30 lb.) pressure. The reduction is rapid and exothermic. In 1 to 2 hours the theoretical amount of hydrogen (0.5 mole) is taken up and absorption ceases (Note 3).

The reaction mixture is filtered through a Hirsch or Büchner funnel, and the bottle is rinsed with 50 ml. of benzene, which is also poured through the funnel. The filtrate is washed with two 50-ml. portions of 10% sodium chloride solution and three 25-ml. portions of water (Note 4). The washings are extracted with three 10-ml. portions of benzene, and the combined benzene solutions are distilled under reduced pressure from a 250-ml. modified Claisen flask. The yield of ethyl *n*-butylcyanoacetate, b.p. 108–109°/9 mm., is 79–81 g. (94–96%, based on the ethyl cyanoacetate used) (Note 5).

2. Notes

1. Ethyl cyanoacetate was purchased from the Dow Chemical Company, Midland, Michigan, and redistilled before using.

2. The palladium on carbon catalyst was prepared by the following method, developed by Walter H. Hartung, School of Pharmacy, University of Maryland, Baltimore. Ten milliliters of a commercial palladium chloride solution containing 0.1 g. of palladium and approximately 0.05 g. of hydrogen chloride per milliliter (obtained from the J. Bishop Company, Malvern, Pennsylvania) is added to a solution of 27 g. of sodium acetate trihydrate in 100 ml. of water. Norite (9 g.) is added, and the mixture is hydrogenated until absorption ceases. The catalyst (10 g.) is filtered on a Büchner funnel, washed with water, dried by drawing air through the funnel for about 30 minutes, and stored in a desiccator over calcium chloride. The palladium catalysts, prepared as described elsewhere in this volume, are presumably also satisfactory for the reductive alkylation described above (p. 77).

3. It is advisable to start the reduction as soon as the reactants are mixed. The yield dropped to 87% when the reaction mixture was allowed to stand for 3 hours before hydrogenating.

4. If an emulsion is formed, it can be broken by adding a few drops of alcohol or several milliliters of ether.

5. Ethyl ethylcyanoacetate and ethyl propylcyanoacetate have been prepared by the same method in yields of 85 and 94%, respectively. Other aldehydes and ketones have been used under slightly different conditions to prepare other ethyl monoalkylcyanoacetates.²

3. Methods of Preparation

Ethyl *n*-butylcyanoacetate has been prepared by alkylation of the sodium enolate of ethyl cyanoacetate with butyl bromide³ and by condensation of capronitrile with ethyl carbonate,⁴ in addition to the method given above.²

References

¹ *Org. Syntheses Coll. Vol. 1*, 61 (1941).

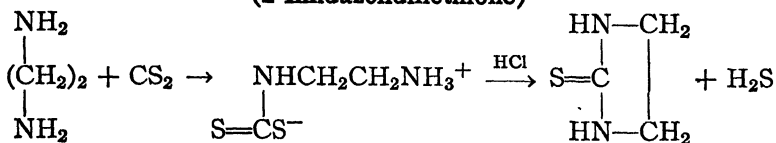
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ETHYLENE THIOUREA

(2-Imidazolidinethione)



Submitted by C. F. H. ALLEN, C. O. EDENS, and JAMES VANALLAN.
 Checked by R. L. SHRINER and CURTIS D. SNOW.

1. Procedure

In a 2-l. round-bottomed flask are placed 120 g. (1.83 moles) of 92% ethylenediamine (Note 1), 300 ml. of 95% ethanol, and 300 ml. of water. The flask is attached to an efficient reflux condenser, and 121 ml. of carbon disulfide is placed in a separatory funnel attached to the top of the condenser by means of a notched cork. About 15 to 20 ml. of the carbon disulfide is added, and the flask is shaken to mix the contents. A vigorous reaction takes place (Note 2), and it may be necessary to cool the flask. After the reaction has started, a water bath at 60° is placed under the flask and the balance of the carbon disulfide is added at such a rate that the vapors reflux about one-third the way up the condenser. About 2 hours are required for the addition of the carbon disulfide. At this time the bath temperature is raised to about 100°, and the mixture is allowed to reflux for 1 hour. Then 15 ml. of concentrated hydrochloric acid is added, and the mixture is refluxed under a good hood (bath at 100°) for 9 to 10 hours. The mixture is cooled in an ice bath, and the product is filtered by suction on a Büchner funnel and washed with 200-300 ml. of cold acetone (Note 3). A yield of 156-167 g. (83-89%) of white crystals is obtained melting at 197-198° (Note 4).

2. Notes

1. If commercial ethylenediamine is used, it should be redistilled. The concentration of the ethylenediamine may be deter-

mined by titration with standard acid and the proper amount taken.

2. Care should be exercised to make certain that the reaction starts, before an additional quantity of carbon disulfide is added. In one experiment in which the carbon disulfide was added all at once, a very violent reaction occurred.

3. Since all the likely contaminants are readily volatile, extensive washing is unnecessary.

4. This product is pure enough for most purposes. It gives no precipitate with copper sulfate solution, indicating the absence of the open-chain acid.¹

3. Methods of Preparation

The only practical method for preparing alkylene thioureas is by the action of the diamines upon carbon disulfide in aqueous alcohol.^{1,2,3,4,5} The final heating is essential to convert the thio-carbamic acid into the cyclic compound, the addition of hydrochloric acid being beneficial.³

References

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² Hofmann, *Ber.*, **5**, 242 (1872).

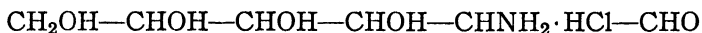
³ Johnson and Edens, *J. Am. Chem. Soc.*, **64**, 2707 (1942).

⁴ Schack, *Arch. Pharm.*, **235**, 442 (1897).

⁵ Klut, *Arch. Pharm.*, **240**, 675 (1902).

***d*-GLUCOSAMINE HYDROCHLORIDE**

Crab shells \rightarrow Chitin \rightarrow



Submitted by EARL R. PURCHASE and CHARLES E. BRAUN.

Checked by H. R. SNYDER and NELSON R. EASTON.

1. Procedure

Two hundred grams of cleaned and dried crab shells (Note 1) ground to a fine powder is placed in a 2-l. beaker, and an excess of dilute (approximately 6 *N*) commercial hydrochloric acid is added slowly to the powdered material until no further action is evident. Much frothing occurs during the addition of the acid, and care must be exercised to avoid loss of material due to foaming over the sides of the beaker. After the reaction has subsided, the reaction mixture is allowed to stand from 4 to 6 hours to ensure complete removal of calcium carbonate. The residue is then filtered, washed with water until neutral to litmus, and dried in an oven at 50–60°. The weight of dried chitin is usually about 70 g., but with some lots of crab shells it may be as low as 40 g.

To 40 g. of dry chitin in a 500-ml. beaker is added 200 ml. of concentrated hydrochloric acid (C.P., sp. gr. 1.18), and the mixture is heated on a boiling water bath for 2.5 hours with continuous mechanical agitation. At the end of this time solution is complete, and 200 ml. of water and 4 g. of Norite are added. The beaker is transferred to a hot plate, and the solution is maintained at a temperature of about 60° and is stirred continuously during the process of decolorization. After an hour the solution is filtered through a layer of a filter aid such as Filter-Cel. The filtrate is usually a pale straw color; however, if an excessive color persists, the decolorization may be repeated until the solution becomes almost colorless. The filtrate is concentrated under diminished pressure at 50° until the volume of the solution is 10–15 ml. The white crystals of glucosamine hydrochloride are

washed onto a sintered glass filter with 95% alcohol. The white crystalline product, after being washed with 95% alcohol and dried, weighs 24–28 g. (60–70% of the weight of the chitin used). The optical rotation of a stable solution of the product containing the α - and β -isomers at equilibrium, $[\alpha]_D^{25.5^\circ}$, varies from $+68.8^\circ$ to $+70.1^\circ$ ($c = 4.75$ in water).

The product is pure enough for most uses. If a purer product is desired, the crystals may be dissolved in the minimum amount of boiling water and treated with Norite. The resulting solution is filtered and added to a large excess of 95% alcohol and stirred vigorously for several hours. The product is collected after 4 to 6 hours. An appreciable amount of the β -form of the amino sugar remains dissolved in the alcohol and may be precipitated by adding ether.

2. Note

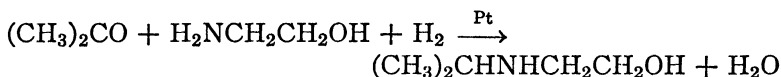
1. The cleaned and dried crab shells were obtained from Carter and Lanhardt Company, Eleventh and Main Avenue, S.W., Washington, D. C.

3. Methods of Preparation

The preparation of glucosamine hydrochloride from lobster shells and crab shells by essentially this method has been reported by Irvine, McNicoll, and Hynd¹ and Hudson and Dale.² Other methods involving the use of cicad larvae shells³ and shrimp shells^{4,5} also have been reported.

References

- ¹ Irvine, McNicoll, and Hynd, *J. Chem. Soc.*, **99**, 256 (1911).
- ² Hudson and Dale, *J. Am. Chem. Soc.*, **38**, 1434 (1916).
- ³ Komori, *J. Biochem. Japan*, **6**, 1–20 (1926) [*C. A.*, **21**, 372 (1927)].
- ⁴ van Alphen, *Chem. Weekblad*, **26**, 602 (1929) [*C. A.*, **24**, 2113 (1930)].
- ⁵ Rigby, U. S. pat. 2,040,879 [*C. A.*, **30**, 4598 (1936)].

2-ISOPROPYLAMINOETHANOL**(Ethanol, 2-isopropylamino-)**

Submitted by EVELYN M. HANCOCK and ARTHUR C. COPE.

Checked by NATHAN L. DRAKE and LARRY GREEN.

1. Procedure

The reaction is carried out in a catalytic hydrogenation apparatus similar to the one described by Adams and Voorhees.¹ In a 1-l. reduction bottle are placed 0.5 g. of platinum oxide catalyst¹ and 50 ml. of commercial absolute alcohol. The bottle is connected to a calibrated low-pressure hydrogen tank and alternately evacuated and filled with hydrogen twice. Hydrogen is then admitted to the system until the pressure is 1–2 atmospheres (15–30 lb.), and the bottle is shaken for 20–30 minutes to reduce the platinum oxide (Note 1). The shaker is stopped, air is admitted to the bottle, and a solution of 61.0 g. (1.0 mole) of ethanolamine (Note 2), 75.4 g. (94 ml., 1.3 moles) of acetone, and 100 ml. of absolute alcohol is rinsed into the reduction bottle with 50 ml. of absolute alcohol. The bottle is alternately evacuated and filled with hydrogen twice. Hydrogen is admitted to the system until the pressure is approximately 25 lb., and the bottle is shaken until the pressure drop indicates that the theoretical amount (1 mole) of hydrogen has been taken up and absorption ceases (6 to 10 hours). Air is admitted to the bottle, and the catalyst is removed by filtration through a Hirsch funnel with a filter plate of small diameter (Note 3). The bottle is rinsed with a total of 75 ml. of benzene, which is also poured through the funnel. The filtrate is rinsed into a 500-ml. modified Claisen flask with 25 ml. of benzene, and most of the solvent is distilled at atmospheric pressure. Distillation of the residue under re-

duced pressure yields 97–98 g. of 2-isopropylaminoethanol, b.p. 86–87°/23 mm. (94–95%, based on the ethanolamine used) (Note 4).

2. Notes

1. If hydrogenation of the reaction mixture is begun in the presence of platinum oxide, a long induction period or lag occurs before the catalyst is reduced.

2. Commercial ethanolamine (Carbide and Carbon Chemicals Corporation) was dried by distillation with a small amount of benzene and redistilled; b.p. 70–72°/12 mm.

3. The usual precaution was observed of keeping the catalyst wet with the solution being filtered to prevent ignition of the filter paper.

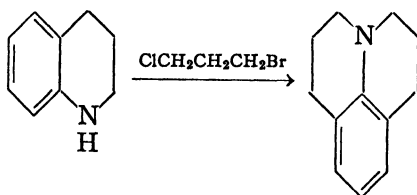
4. Similar procedures have been used in preparing other 2-alkylaminoethanols² and N-alkyl derivatives of 1-amino-2-propanol, 2-amino-1-propanol, 3-amino-1-propanol, 2-amino-1-butanol, and 1-amino-2-methyl-2-propanol.³

3. Methods of Preparation

2-Isopropylaminoethanol has been prepared by the reaction of isopropylamine with ethylene oxide⁴ and by the method given above.²

References

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- ² Cope and Hancock, *J. Am. Chem. Soc.*, **64**, 1503 (1942).
- ³ Cope and Hancock, *J. Am. Chem. Soc.*, **66**, 1453 (1944); Hancock and Cope, *J. Am. Chem. Soc.*, **66**, 1738 (1944); Hancock, Hardy, Hely, Wright, and Cope, *J. Am. Chem. Soc.*, **66**, 1747 (1944).
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JULOLIDINE**(Benzo[*ij*]quinolizine, 1,2,3,5,6,7-hexahydro-)**

Submitted by D. B. GLASS and A. WEISSBERGER.
Checked by CLIFF S. HAMILTON and CAROL K. IKEDA.

1. Procedure

A mixture of 66.5 g. (0.5 mole) of tetrahydroquinoline and 400 g. of trimethylene chlorobromide (Note 1) is placed in a 1-l. round-bottomed flask attached to a reflux condenser, and heated in an oil bath held at 150–160° for 20 hours (Note 2). The reaction mixture is cooled, a solution of 50 ml. of concentrated hydrochloric acid in 500 ml. of water is added, and the excess trimethylene chlorobromide is removed by distillation with steam (Note 3). The acid residue from the steam distillation is made alkaline with a 40% solution of sodium hydroxide (about 75 ml.), and the julolidine is extracted with two 150-ml. portions of ether. The ethereal solution is washed with 150 ml. of water and dried over sodium hydroxide pellets. The ether is evaporated and the residue distilled under reduced pressure. The portion that boils at 105–110°/1 mm. is collected (Notes 4 and 5). The yield is 67–70 g. (77–81%).

2. Notes

1. The tetrahydroquinoline and trimethylene chlorobromide were Eastman grade materials of the Eastman Kodak Company.
2. The heating should be carried out in a hood, or a gas trap

should be used to remove the hydrogen halides that are evolved.

3. The trimethylene chlorobromide recovered may be dried over calcium chloride and used in a subsequent run.

4. The julolidine solidifies in the receiver, m.p. 39–40°.

5. After standing in contact with air for several weeks, the julolidine may become colored by the formation of a red compound. This red compound may be removed by distillation or by dissolving the amine in 2 or 3 volumes of hexane, treating the hexane solution with Norite or Darco, and filtering. The julolidine is crystallized from the hexane solution by cooling in an acetone-Dry Ice bath. The resulting product melts at 39–40° and amounts to 85–90% of the original.

3. Methods of Preparation

Julolidine has been prepared by the reaction of trimethylene chlorobromide with formanilide,¹ aniline,¹ methylaniline,¹ and tetrahydroquinoline;^{1,2} by the reduction of 8,10-diketojulolidine;¹ by the intramolecular condensation of N-(γ -bromopropyl)-tetrahydroquinoline;³ and by dehydration of N-(γ -hydroxypropyl)-tetrahydroquinoline or di-(γ -hydroxypropyl)-aniline with phosphorus pentoxide.⁴

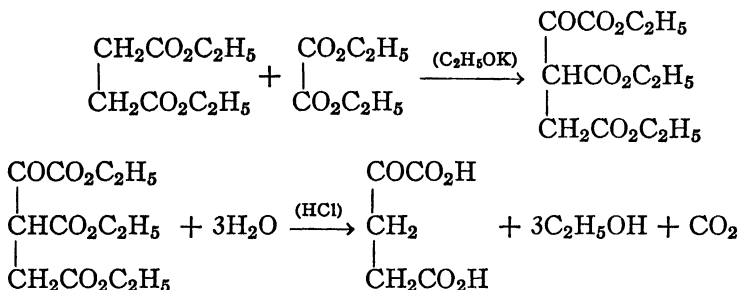
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⁴ Rindfusz and Harnack, *J. Am. Chem. Soc.*, **42**, 1724 (1920).

α -KETOGLUTARIC ACID(Glutaric acid, α -oxo-)

Submitted by LESTER FRIEDMAN and EDWARD KOSOWER.

Checked by REYNOLD C. FUSON and ELLIOTT N. MARVELL.

1. Procedure

A. *Ethyl oxalylsuccinate*. Potassium (39.5 g., 1 gram atom) is cut into pieces under xylene (Note 1) in a wide evaporating dish. The xylene is poured off, and the metal is washed with three 50-ml. portions of absolute ether. The potassium is then transferred quickly to a 2-l. three-necked flask containing 650 ml. of anhydrous ether and fitted with a reflux condenser, a mercury-sealed mechanical stirrer (Note 2), and a dropping funnel containing 150 ml. of anhydrous ethanol. The alcohol is added over a period of about 1.5 hours; stirring is unnecessary. After most of the alcohol has been added, the flask is heated on a water bath to ensure complete solution of the potassium. This usually takes from 3 to 4 hours. After the reaction is completed, the flask is cooled to room temperature, and 146 g. (1 mole) of ethyl oxalate is added rapidly through the dropping funnel, with stirring, to the solution of potassium ethoxide in ether. A yellow color develops at this point. The stirring is continued for an additional 10 minutes. Then 174 g. (1 mole) of ethyl succinate is added rapidly, with vigorous stirring (Note 3). After a few minutes,

the potassium salt crystallizes, making further stirring impracticable. It is collected on a filter and washed with ether until the salt is colorless.

The salt is dissolved in 270 ml. of water, and 100 ml. of concentrated hydrochloric acid is added. The ethyl oxalylsuccinate separates as an oil and rises to the surface. It is removed by extracting the mixture with 100-ml. portions of ether until the aqueous solution is almost colorless. The extracts are dried over sodium sulfate, and the ether is distilled under reduced pressure. The ethyl oxalylsuccinate remains in the flask as a yellow oil. The yield is 225–227 g. (82–83%) (Note 4).

B. *α -Ketoglutaric acid*. The ester obtained by the foregoing procedure is mixed with 600 ml. of concentrated hydrochloric acid and left overnight. The mixture is concentrated by distillation (Note 5) until the temperature of the liquid reaches 140°. It is poured into an evaporating dish and allowed to cool. The solid mass, weighing 110–112 g., is then pulverized. The yield of α -ketoglutaric acid is 92–93% of the theoretical for the last step, or 75–77% based upon diethyl succinate. The light tan product, obtained as described above, is suitable for most purposes, but a purer acid, m.p. 109–110° (corr.) may be obtained by recrystallization from an acetone-benzene mixture.

2. Notes

1. All containers must be absolutely dry, and anhydrous xylene must be used. Important! Destroy with anhydrous ethanol all potassium remaining in the xylene and waste ether.

2. The stirrer is not necessary until the ethyl oxalate is added. The submitters found the use of a nitrogen atmosphere to be unnecessary.

3. The ethyl oxalate was redistilled, and the fraction boiling at 106–107°/25 mm. was used. The ethyl succinate was C.P. material obtained from Eimer and Amend and was used without further purification.

4. For further purification, the product can be distilled at about 115°/1 mm.

5. This should be done in a hood, or a trap should be used to remove the hydrochloric acid.

The submitters wish to thank Mr. Andrew Streitweiser for his invaluable assistance.

3. Methods of Preparation

Ethyl oxalysuccinate has been prepared by the condensation of ethyl oxalate with ethyl succinate in the presence of sodium ethoxide¹ or of potassium ethoxide.² The method described above is somewhat more convenient, and has given a higher yield of a better product, than one based upon sodium ethoxide, submitted by A. E. Martell and R. M. Herbst.

α -Ketoglutaric acid has been prepared by the hydrolysis of ethyl oxalysuccinate with concentrated hydrochloric acid;³ by the distillation of ethyl oxalysuccinate with concentrated hydrochloric acid;⁴ by treating α,β -dibromoglutaric acid with 2 *N* sodium carbonate solution;⁵ by treatment of ethyl α -bromoglutaconate with alkalis;⁶ and by treating ethyl α,α' -dibromoglutarate with alcoholic potash.⁷

References

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² Wislicenus, *Ber.*, **44**, 1567 (1911).

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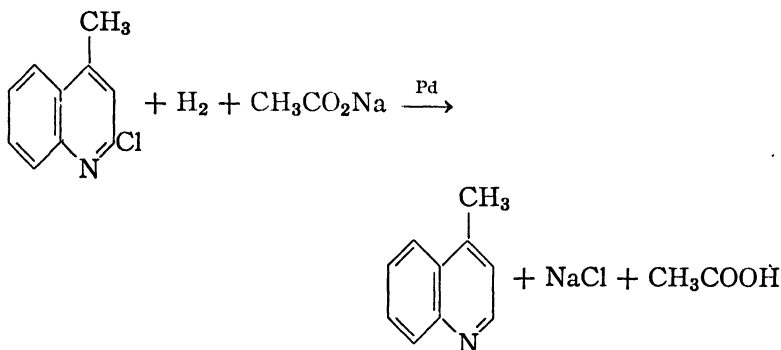
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LEPIDINE



Submitted by FRED W. NEUMANN, NOLAN B. SOMMER, C. E. KASLOW,
and R. L. SHRINER.

Checked by CLIFF S. HAMILTON and ROBERT F. COLES.

1. Procedure

In a 500-ml. Erlenmeyer flask are placed 20 g. (0.11 mole) of pure 2-chlorolepidine¹ (Note 1), 9.3 g. (0.11 mole) of powdered anhydrous sodium acetate, and 200 ml. of glacial acetic acid. The mixture is heated to about 70° and shaken until solution is complete. The solution is transferred to a pressure bottle of an apparatus for catalytic reduction,² equipped with a heating element and a variable resistance. The flask is rinsed with two 10-ml. portions of hot glacial acetic acid. Then 3 g. of palladium on carbon is added (Note 2), the bottle is attached to the shaking machine, and the variable resistance is adjusted until the temperature of the liquid is between 55° and 70° (Note 3). The bottle is swept out with hydrogen, an initial pressure of about 1.8–2.2 atmospheres (26–33 lb.) is applied, and the shaking is started. Hydrogen absorption is rapid during the first 15 minutes and then gradually slackens; the theoretical amount is absorbed in 1.5–2 hours. To ensure complete reduction, shaking is continued an additional 30 minutes. The warm acid solution is separated

from the catalyst by filtration through a 1- to 2-mm. layer of Norite on a Büchner funnel. The bottle and funnel are washed with three 30-ml. portions of glacial acetic acid. The acetic acid is removed from the combined filtrates by heating to 70° under reduced pressure (water pump, 25 mm.). The residue is dissolved in 50 ml. of water and transferred to a 500-ml. separatory funnel, an additional 25 ml. of water being used for washing. The water solution is made basic to litmus with 30% sodium hydroxide (about 40–100 ml.) and extracted with one 100-ml. portion of ether and then with two 50-ml. portions. The ether extracts are combined and dried overnight with about 30 g. of solid potassium hydroxide. The ether is removed by distillation from a 250-ml. flask, and the residue is transferred to a modified 50-ml. distilling flask (Note 4), three 5-ml. portions of anhydrous ether being used to ensure complete transference. After the ether is removed, the residue distills at 126–127°/14–15 mm. The product is colorless, water clear, and weighs 13–14 g. (81–87%) (Notes 5 and 6).

2. Notes

1. Pure 2-chlorolepidine, m.p. 58–59°, should be used.

2. The catalyst is previously prepared in an apparatus for catalytic hydrogenation,² in which are placed 0.5 g. of palladous chloride, 3.0 g. of Norite, and 20 ml. of distilled water. The bottle is swept out with hydrogen and then shaken with hydrogen for 2–3 hours at 2–3 atmospheres (40 lb.) pressure. The palladium on carbon is collected on a Büchner funnel, washed with five 50-ml. portions of distilled water, then with five 50-ml. portions of 95% ethanol, and finally twice with ether. Upon drying, about 3 g. of the catalyst is obtained. It is stored in a vacuum desiccator over solid sodium hydroxide. If the reduction of the chlorolepidine does not proceed normally, the used catalyst should be removed by suction filtration and a fresh 3-g. portion of catalyst added. Failure of the reduction step is usually due to an inactive catalyst or to impurities in the acetic acid or chlorolepidine. The palladium catalysts, prepared as described elsewhere in this volume, are presumably also satisfactory for the reduction of 2-chlorolepidine (p. 77).

3. The reduction does not proceed smoothly at room temperature with the palladium catalyst. Raney nickel may be used as a catalyst with ethanol containing potassium hydroxide at room temperature, but about 15 hours are required for reduction.

4. The submitters used a special flask having the shape and dimensions shown in Fig. 1. The two necks were wrapped with

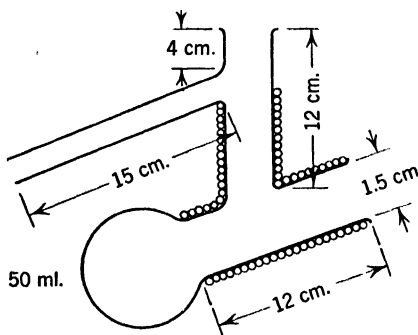


FIG. 1.

asbestos cord. The checkers used an ordinary Claisen flask (50 ml.).

5. By distillation of the crude product from four runs, a yield of 92% was obtained.

6. The submitters have followed the same procedure in preparing the compounds listed below from the corresponding 2-chloro derivatives. The ether extractions and distillation steps were omitted when solid products were obtained.

COMPOUND	PRODUCT		B.P. OR M.P.
	% CRUDE	% PURIFIED	
6-Methylepidine	100	87	b.p. 137°/12 mm.
8-Methylepidine	94	90	m.p. 54-55°
5,8-Dimethylepidine	96	86	b.p. 154-56°/13 mm.
6,8-Dimethylepidine	100	91	m.p. 55-56°
6-Methoxylepidine monohydrate	100	80	m.p. 50-52°
5,8-Dimethoxylepidine	98	90	m.p. 94-95°
2-Methyl-6-methoxyquinoline *	96	..	m.p. 62-65°

* From 2-methyl-4-chloro-6-methoxyquinoline.

3. Methods of Preparation

The process described above is essentially that of Ainley and King,³ who prepared 6-methoxylepidine. Lepidine has also been prepared by the reduction of 2-chlorolepidine with hydrogen and Raney nickel,⁴ with tin and hydrochloric acid,^{5,6,7} and with concentrated hydroiodic acid and red phosphorus;⁸ by the reduction of 2-iodolepidine with iron and dilute sulfuric acid;⁹ by the zinc-dust distillation of 2-hydroxy-4-methyl quinoline under reduced pressure¹⁰ or of 2-hydroxy-3-cyano-4-methyl quinoline;¹¹ by the distillation of 1,2,3,4-tetrahydroquinoline-4-carboxylic acid with zinc dust in a stream of hydrogen;¹² by the decarboxylation of 4-methylquinoline-2-carboxylic acid,¹³ by leading vapors of aniline and crotonaldehyde over a contact catalyst at above 500°;¹⁴ by heating aniline and vinyl methyl ketone with sulfuric acid and nitrobenzene;¹⁵ by heating aniline and β -hydroxyethyl methyl ketone in the presence of concentrated sulfuric acid and nitrobenzene¹⁶ or in the presence of aniline hydrochloride and ethanol;¹⁷ by heating aniline and β -chloroethyl methyl ketone in the presence of concentrated hydrochloric acid and nitrobenzene or arsenic acid^{18,19} or in the presence of aniline hydrochloride, ethanol, and nitrobenzene;²⁰ by heating a mixture of acetone, formaldehyde, and aniline hydrochloride;^{21,22} by passing vapors of acetylene and aniline over aluminum oxide at 360–420°;²³ and by passing vapors of aniline and acetaldehyde or paraldehyde over aluminum oxide in a copper tube at 480°.²⁴ Campbell and Schaffner²⁵ have recently described the preparation of lepidine in 70–73% yields by the reaction of aniline hydrochloride with methyl vinyl ketone or 1,3,3-trimethoxybutane or 1-methoxy-3-butanone in alcohol in the presence of ferric or zinc chloride.

References

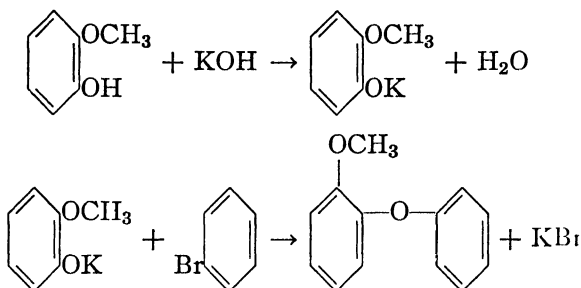
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- ¹⁹ Schering-Kahlbaum A.-G., British pat. 283,577 [*C. A.*, **22**, 4132 (1928)].
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- ²² Beyer, *J. prakt. Chem.*, [2] **33**, 418 (1885).
- ²³ Tschitschibabin, *J. Russ. Phys. Chem. Soc.*, **47**, 713 (1915); *Chem. Zentr.*, **1916**, I, 920 (Beilstein, "Handbuch der organischen Chemie," 4th ed., Suppl. I, **20**, 150, J. Springer, Berlin, 1935).
- ²⁴ Tschitschibabin, Ger. pat. 468,303 [*C. A.*, **23**, 607 (1929)].
- ²⁵ Campbell and Schaffner, *J. Am. Chem. Soc.*, **67**, 86 (1945).

2-METHOXYDIPHENYL ETHER**(Benzene, 1-methoxy-2-phenoxy-)**

Submitted by H. E. UNGNADE and E. F. ORWOLL.

Checked by HOMER ADKINS and E. E. BURGOYNE.

1. Procedure

Powdered potassium hydroxide (29.4 g., 0.52 mole) is placed in a 500-ml. round-bottomed flask. Guaiacol (75 g., 0.60 mole) is added, and the mixture is allowed to react exothermically. After the reaction is complete, the mixture is stirred with a glass rod and then heated under reduced pressure for 3 hours at 150° in an oil bath (Note 1).

To the dry salt is added 0.3 g. of copper powder (Note 2), 81 g. (0.51 mole) of bromobenzene, and a few drops of guaiacol (Note 3). The mixture is stirred thoroughly with a glass rod; the flask is fitted with an air condenser and heated in a metal bath (Note 4). A reaction becomes evident at a bath temperature of 160–180°, liquefaction occurs, and the color of the mixture changes to red or purple. The temperature is gradually raised to 200° and maintained at 200° for 2 hours.

After cooling, the products are extracted from the reaction mixture with successive portions of water and ether. Extraction is facilitated by breaking up the solid material with a glass rod. The total amounts of solvents required are approximately 750 ml.

of water and 150 ml. of ether. The combined ether and water solutions are transferred to a 3-l. round-bottomed flask and steam-distilled with superheated steam maintained at 180–200°. After removal of the ether, 300 ml. of distillate is collected. This distillate contains the unreacted starting materials. Continued distillation gives 64–69 g. (62–67%) of crude solid 2-methoxydiphenyl ether in 14 l. of distillate. The product is filtered with suction and dried. Crystallization from a mixture of 600 ml. of low-boiling petroleum ether (b.p. 30–60°) and 435 ml. of higher-boiling petroleum ether (b.p. 60–70°) yields 54–61 g. of 2-methoxydiphenyl ether melting at 77–78°. Other 2-methoxydiphenyl ethers have been prepared by this procedure (Note 5).

2. Notes

1. The salt of guaiacol is heated under reduced pressure, in order to remove water, which is a negative catalyst in the Ullmann reaction.¹

2. The copper catalyst may be prepared by the method of Brewster and Groening.²

3. An excess of guaiacol is essential. Weston and Adkins¹ have found that the phenol, copper, and air form the active catalyst in the Ullmann reaction.

4. The checkers used an electrically heated oil bath.

5. Yields of 54% of 2-methoxy-4'-methyl diphenyl ether from *p*-bromotoluene and guaiacol, and 60% of 2-methoxy-5-methyl diphenyl ether from 3-bromo-4-methoxytoluene and phenol, have been obtained by the same method in the laboratory of the submitters.

3. Methods of Preparation

The procedure above is a modification of the method of Ullmann and Stein³ for the same compound. Sartoretto and Sowa⁴ used the same general method. The need for a catalyst can be avoided by heating a mixture of guaiacol potassium, guaiacol, and chlorobenzene at 200° under pressure.⁵ Ullmann and Stein⁶ have prepared the compound by using phenol, *o*-bromoanisole,

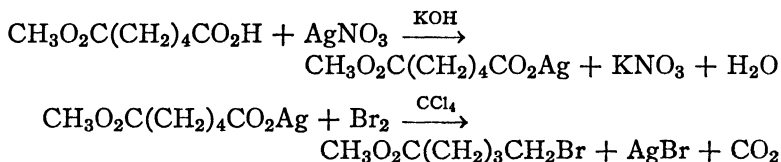
copper powder, and potassium hydroxide. 2-Hydroxydiphenyl ether can be converted to the methoxy derivative by treating it with methyl alcohol, methyl iodide, and potassium hydroxide.⁷

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METHYL 5-BROMOVALERATE

(Valeric acid, δ -bromo-, methyl ester)



Submitted by C. F. H. ALLEN and C. V. WILSON.

Checked by CLIFF S. HAMILTON and NOBORU TOSAYA.

1. Procedure

To a solution of 33 g. (0.5 mole) of potassium hydroxide (Note 1) in 1.5 l. of distilled water in a 5-l. flask or other appropriate container fitted with a mechanical stirrer is added 80 g. (0.5 mole) of methyl hydrogen adipate (Note 2). With continuous stirring a solution of 85 g. (0.5 mole) of silver nitrate in 1 l. of distilled water is added rapidly (about 15 minutes). The precipitated methyl silver adipate is collected on a Büchner funnel, washed with methanol, and dried in an oven at 50–60°. For the next step the dried silver salt is finely powdered and sieved through a 40-mesh screen. The combined yield from two such runs is 213 g. (80%).

The 213 g. (0.8 mole) of finely powdered silver salt is placed in a 1-l. three-necked flask (Note 3); two necks of the flask are stoppered, and the third is connected to a water pump through a U-tube or flask containing Drierite. The flask is then placed in an oil bath and evacuated to a pressure of about 15 mm. The temperature of the oil bath is maintained at 100–110° for 36 hours (Notes 4 and 5).

The pressure in the flask is restored to that of the atmosphere. The flask is removed from the oil bath and equipped with a dropping funnel, condenser, and mechanical stirrer (Note 6). To the salt is added 350 ml. of dry carbon tetrachloride (Note 7); the stirrer is started, and 117 g. (40 ml., 0.73 mole) of dry bromine¹ is added through the dropping funnel over a 30- to 40-minute period. Occasional cooling may be necessary as the reaction is quite vigorous at first. When all the bromine has been added, the mixture is heated for 1 hour on a steam bath. It is then filtered and the silver bromide washed thoroughly on the filter with 100 ml. of warm carbon tetrachloride. The filtrate is washed once with 100 ml. of 10% sodium carbonate solution and dried over 30–40 g. of Drierite. The solvent is removed and the residue distilled under reduced pressure. The yield of product boiling at 75–80°/4 mm. is 101–106 g. The yield is 65–68% based on the weight of the methyl silver adipate before drying under reduced pressure, or 52–54% based upon methyl hydrogen adipate.

2. Notes

1. Reagent grade potassium hydroxide containing 85% potassium hydroxide is used.

2. The methyl hydrogen adipate was Eastman Kodak grade.

3. Drying is carried out in the flask in which the final reaction is to be run in order to avoid a transfer. The success of this preparation depends upon the exclusion of moisture. The silver salt retains traces of water tenaciously.

4. If the indicated pressure is maintained the water pump may be disconnected, but owing to leaks it will usually be found necessary to re-evacuate several times over the 36-hour period.

5. A good "vacuum oven" would serve for drying just as well, but the temperature of the salt should not exceed 110°.

6. For best results all equipment should be thoroughly dried.

7. The carbon tetrachloride is dried over phosphorus pentoxide or some other drying agent.

3. Methods of Preparation

This method with some slight modifications is applied in the synthesis of ω -bromo esters from C₅ to C₁₇.² Methyl 5-bromovalerate has been prepared by treating the silver salt of methyl hydrogen adipate with bromine.² The ethyl ester has been prepared from the acid by esterification^{3,4} or through the acid chloride.⁴

References

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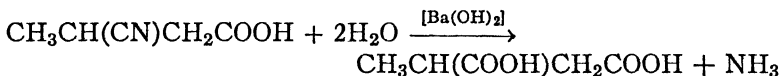
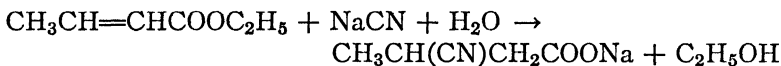
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METHYLSUCCINIC ACID

(Pyrotartaric acid)



Submitted by GEORGE BOSWORTH BROWN.

Checked by LEE IRVIN SMITH and VINCENT J. WEBERS.

1. Procedure

The procedure should be carried out under a hood since the poisonous hydrogen cyanide may be evolved.

In a 3-l. flask provided with a reflux condenser are placed 114 g. (1.0 mole) of ethyl crotonate (Note 1), 460 ml. of 95%

ethanol, and a solution of 54 g. (1.06 moles) of 95% sodium cyanide in 128 ml. of water. The solution is refluxed on a steam bath for 5 hours, during which time some ammonia is evolved and the solution becomes dark yellow. A suspension of 150 g. of barium hydroxide octahydrate in 286 ml. of hot water is added to the solution, and the mixture is concentrated under reduced pressure (about 30 mm.) to a volume of about 400 ml. It is again refluxed on the steam bath for 4 hours or until the evolution of ammonia almost ceases (Note 2). The solution is then concentrated to a thick paste under reduced pressure.

The residuc is cooled and dissolved in 171 ml. of nitric acid (sp. gr. 1.4) (Note 3), and the solution is warmed for 30 minutes on the steam bath. It is immediately concentrated to complete dryness under reduced pressure (Note 4). The flask is cooled, 300 ml. of benzene is added, and the mixture is refluxed for a short time to render the cake friable. The benzene is removed by decantation, and the cake is pulverized and extracted six times by refluxing it briefly with 300-ml. portions of ether. The combined benzene and ether extracts are filtered and concentrated to a volume of about 225 ml. In the meantime the residual salts are extracted twice by refluxing them vigorously for a short time with 300-ml. portions of benzene. The benzene solutions are separated by decantation and added to the ether concentrate. The distillation is then continued until about two-thirds of the benzene has been removed, when the benzene solution is poured into a beaker and allowed to cool. The methylsuccinic acid is collected on a filter and is washed by shaking a suspension of it in 150 ml. of chloroform (Note 5). The yield of air-dried product, melting at 110–111°, amounts to 87–93 g. (66–70%) (Note 6).

2. Notes

1. Ethyl crotonate may be prepared readily from technical crotonic acid by action of sulfuric acid and alcohol. The checkers obtained 72% yield both by the ordinary procedure and by the method of azeotropic distillation.

2. The checkers refluxed the mixture for 8 hours at this point;

traces of ammonia were still present. Most of the ammonia was evolved in 4 hours, however.

3. The excess nitric acid is used in order to oxidize unchanged crotonic acid. Since hydrocyanic acid may be evolved the operation should be carried out under a hood.

4. The residue must be dry because methylsuccinic acid is extremely soluble in water.

5. If a series of runs is to be made, the chloroform may be used repeatedly.

6. The submitter states that the same percentage yield is obtained when four times the above quantities of reagents are used.

3. Methods of Preparation

Methylsuccinic acid has been prepared by the pyrolysis of tartaric acid;¹ from 1,2-dibromopropane or allyl halides by the action of potassium cyanide followed by hydrolysis;² by reduction of itaconic, citraconic, and mesaconic acids;³ by hydrolysis of ketovalerolactonecarboxylic acid;⁴ by decarboxylation of 1,1,2-propanetricarboxylic acid;⁵ by oxidation of β -methylcyclohexanone;⁶ by fusion of gamboge with alkali;⁷ by hydrogenation and condensation of sodium lactate over nickel oxide;⁸ from acetoacetic ester by successive alkylation with a methyl halide and a monohaloacetic ester;⁹ by hydrolysis of α -methyl- α' -oxalosuccinic ester¹⁰ or α -methyl- α' -acetosuccinic ester;¹¹ by action of hot, concentrated potassium hydroxide upon methylsuccinaldehyde dioxime;¹² from the ammonium salt of α -methylbutyric acid by oxidation with hydrogen peroxide;¹³ from β -methyllevulinic acid by oxidation with dilute nitric acid¹⁴ or hypobromite;¹⁵ from β -methyladipic acid;¹⁶ and from the decomposition products of glyceric acid¹⁷ and pyruvic acid.¹⁸ The method described above is a modification of that of Higginbotham and Lapworth.¹⁹

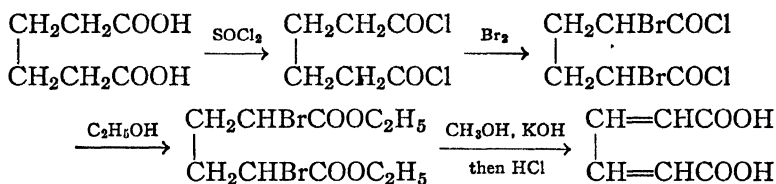
References

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- ¹⁸ Urion, *Ann. chim.*, (11), **1**, 84 (1934).
- ¹⁹ Higginbotham and Lapworth, *J. Chem. Soc.*, **121**, 49 (1922).

MUCONIC ACID



Submitted by P. C. GUHA and D. K. SANKARAN.

Checked by C. F. H. ALLEN and H. W. J. CRESSMAN.

1. Procedure

A. *Diethyl α,δ-dibromoadipate*. In a 3-l. three-necked flask (Note 1) fitted with a reflux condenser, a dropping funnel, and a mechanical stirrer are placed 1 kg. (6.85 moles) of adipic acid and 2 kg. (1220 ml., 16.8 moles) of thionyl chloride (Notes 2 and 3). The mixture is stirred and heated gently on the steam bath until solution is effected, and the evolution of hydrogen chloride (Note 4) ceases after about 3 hours. The excess thionyl chloride

is distilled by heating on a steam bath, the last portion of the reagent being taken off under reduced pressure.

To the acid chloride, mechanically stirred and heated on the steam bath, is added 2.5 kg. (805 ml. 15.6 moles) of dry bromine¹ as rapidly as it will react (Note 5). The addition requires about 12 hours. The contents of the flask are stirred and heated an additional 2 hours, transferred to a dropping funnel (Note 6), and added in a thin stream to 5 l. of absolute ethyl alcohol, which has previously been placed in a 12-l. flask provided with a stopper carrying an efficient reflux condenser, a separatory funnel, and a mechanical stirrer. The resulting vigorous reaction is controlled by external cooling. After the dibromoacid chloride has been added, the reaction mixture is allowed to stand at room temperature overnight and is then poured into 5 l. of cold water. The top alcoholic aqueous layer is decanted and extracted once with 8 l. of ether. The oily bottom layer is dissolved in the ether extract, washed first with 1 l. of a 2% sodium bisulfite solution, then with two 1-l. portions of 3% sodium carbonate solution, and finally with several portions of water. The ether solution is dried over 175 g. of potassium carbonate; the solvent is distilled on the steam bath. The yield of residual ester (Note 7) amounts to 2260–2400 g. (91–97% of the theoretical amount).

B. *Muconic acid.* To a solution of 3 kg. of potassium hydroxide and 5 l. of methyl alcohol (Note 8) in a 12-l. flask, equipped as described above, is added in a thin stream from a separatory funnel (Note 6), and with stirring, 1130 g. (3.14 moles) of diethyl α,δ -dibromoadipate. The ester is heated on the steam bath to nearly 100° before it is added. The addition is so regulated as to permit rather vigorous refluxing and requires 45 minutes. Heating on the steam bath and stirring are continued an additional 2 hours. The mixture is allowed to stand at room temperature overnight and is cooled. The potassium muconate and potassium bromide are filtered (Note 9), washed on the funnel with two 350-ml. portions of methyl alcohol and 400 ml. of ether, transferred without further drying to an enameled 11- to 12-l. pail, and dissolved in 8 l. of hot water. The aqueous solution, to which is added 30 g. of decolorizing carbon,

Norite, is heated to boiling by introduction of steam, filtered through a Norite filter pad by suction, and cooled in an ice-salt bath. The muconic acid is precipitated by the addition of a large excess (1500 ml.) (sp. gr. 1.18) of concentrated hydrochloric acid to the cold solution. The acid is added in a thin stream to the well-stirred solution. After 2 hours the muconic acid is filtered, washed first with two 400-ml. portions of cold water and then with 200 ml. of methyl alcohol, and dried at 85°. The yield of nearly colorless product melting at 296–298°, with decomposition, amounts to 165–195 g. (37–43%).

2. Notes

1. Apparatus with ground-glass joints is preferable.
2. The yield obtained in molar-sized runs is also about 40% of the theoretical.
3. The submitters used 1 mole of adipic acid and added 2 moles of phosphorus pentachloride in 20-g. portions over an interval of 30 minutes.
4. The considerable quantities of hydrogen chloride and hydrogen bromide evolved are best handled by means of a gas-absorption trap.² The insertion of a calcium chloride tube between the trap and the reflux condenser is recommended.
5. The bromine is added as rapidly as it will react but not so rapidly that loss occurs through the condenser. A photoflood lamp accelerates the rate of bromination.
6. The dibromoacid chloride solidifies at room temperature. It is advisable to heat the funnel by means of a coil of copper tubing through which steam is passed.
7. Two isomers, a solid and a liquid, are formed during the bromination and subsequent esterification.
8. A commercial grade of methanol was used; absolute methanol did not result in an increased yield.
9. A pad of Filter-Cel aids in the slow filtration. About 100 g. is needed with a 30-cm. funnel.

3. Methods of Preparation

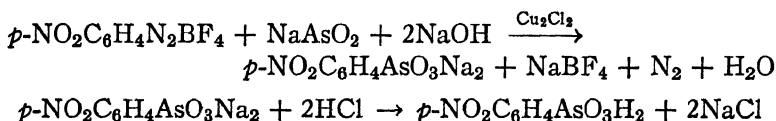
Muconic acid has been obtained in a variety of ways. The procedures that seem most important from a preparative point of view are by treatment of ethyl α,δ -dibromoadipate with alcoholic potassium hydroxide,^{3,4} by condensation of glyoxal (as the sodium bisulfite addition product) with malonic acid,^{5,6} by heating ethyl 1-acetoxy-1,4-dihydromuconate (obtained by condensing ethyl oxalate and ethyl crotonate, acetylating, and reducing),^{7,8} and by oxidation of phenol with peracetic acid.⁹

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p-NITROPHENYLARSONIC ACID

(Benzeneearsonic acid, *p*-nitro-)



Submitted by A. WAYNE RUDDY and EDGAR B. STARKEY.
 Checked by CLIFF S. HAMILTON and RICHARD E. BENSON.

1. Procedure

In a 2-l. beaker provided with an efficient mechanical stirrer, 52 g. (0.4 mole) of sodium metaarsenite and 16 g. (0.4 mole) of

sodium hydroxide are dissolved in 600 ml. of water (Note 1) and 6 g. of cuprous chloride is suspended in the solution.

A mixture of 300 ml. of water and the *p*-nitrobenzenediazonium borofluoride¹ obtained from 0.25 mole of *p*-nitroaniline (Note 2) is added during a period of 1 hour to the sodium arsenite solution. The foaming that accompanies the evolution of nitrogen is readily controlled by the occasional addition of small amounts of ether or benzene (Note 3). As the reaction proceeds, 100 ml. of 10% sodium hydroxide solution (0.25 mole) is added in 20-ml. portions. Stirring is continued for another hour, and then the mixture is warmed to 60° for 30 minutes and filtered with suction through a sintered-glass funnel. The residue on the funnel is washed with two 50-ml. portions of water. To the combined filtrate and washings is added concentrated hydrochloric acid (sp. gr. 1.19) until the solution is acid to litmus paper. The mixture is filtered, activated charcoal is added to the filtrate, and the solution is concentrated to about 350 ml. After the hot solution has been filtered with suction, concentrated hydrochloric acid is added until the solution is acid to Congo red paper. The solution is placed in a refrigerator overnight, and the crystals are collected on a Büchner funnel and washed twice with 20-ml. portions of ice water. The combined filtrates and washings are concentrated to about 150 ml., chilled, and filtered. The total quantity of crystals is dissolved in 10% ammonium hydroxide solution; the solution is filtered and again made acid to Congo red paper with concentrated hydrochloric acid. After the solution has been thoroughly chilled (preferably overnight), the *p*-nitrophenylarsonic acid is filtered on a Büchner funnel and washed with small portions of ice water until free of ammonium chloride. After drying, the yellow crystals melt with decomposition at 298–300°. The yield is 44–48.5 g. (71–79%) (Note 4).

2. Notes

1. The sodium arsenite solution may also be prepared by dissolving 39.6 g. (0.2 mole) of arsenious oxide and 32 g. (0.8 mole) of sodium hydroxide in 600 ml. of water.

2. According to the submitters *p*-nitrobenzenediazonium borofluoride may also be prepared as follows:

p-Nitroaniline (34.5 g.) is dissolved in 63 ml. of concentrated hydrochloric acid (sp. gr. 1.19) and 50 ml. of water. The solution is cooled to 0°, and 17.3 g. of sodium nitrite in 40 ml. of water is added slowly with vigorous stirring. After the diazotization is complete, as indicated by a positive test with starch iodide paper, a solution of 55 g. of sodium fluoborate in 110 ml. of water is added. The thick slurry is stirred for 15 minutes and then filtered with suction and washed with ice water, twice with methanol, and twice with ether. The solid should be sucked as free as possible from liquid after each washing. The compound may be kept in an evacuated desiccator until needed.

3. The checkers found that the foaming is more readily controlled by amyl alcohol than by the addition of ether or benzene.

4. This is a general method for preparing arylarsonic acids. The melting points and yields of other arsonic acids prepared by the submitters are as follows: phenyl, 156°, 58%; *o*-nitrophenyl, 232–234° dec., 67%; *m*-nitrophenyl, 182°, 47%; *o*-tolyl, 159–160°, 63%; *m*-tolyl, 150°, 54%; *p*-tolyl, 300° dec., 73%; *o*-chlorophenyl, 182°, 52%; *p*-chlorophenyl, above 300°, 63%; *o*-carboxyphenyl, above 300°, 65%; *p*-carboxyphenyl, 232° dec., 67%; *p*-carbethoxyphenyl, 260°, 60%; *p*-acetophenyl, 175°, 70%.

3. Methods of Preparation

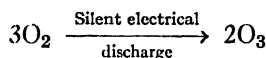
p-Nitrophenylarsonic acid has been prepared by heating *p*-nitrobenzenediazonium chloride with arsenious acid in hydrochloric acid,² by the action of *p*-nitrobenzenediazonium chloride on sodium arsenite,³ by the action of sodium arsenite on sodium *p*-nitrobenzeneisodiazo oxide,⁴ by the diazotization of *p*-nitroaniline in acetic acid in the presence of arsenic chloride and cuprous chloride,⁵ and by the reaction of *p*-nitrobenzenediazonium borofluoride with sodium arsenite in the presence of cuprous chloride.⁶

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OZONE

(A laboratory ozonizer)



Submitted by L. I. SMITH, F. L. GREENWOOD, and O. HUDRLIK.

Checked by R. L. SHRINER, C. E. KASLOW, and R. D. STAYNER.

1. Description of Apparatus and Procedures

A diagrammatic sketch of the complete apparatus for the laboratory production and use of ozone in organic reactions is shown in Fig. 2.

A. Purification train. Oxygen from a cylinder (*A*) fitted with a reducing valve (*B*) is led to a pressure release tube (*C*). This is a T-tube, the long arm of which dips into a test tube of mercury. The height of the mercury column should be about 2 to 3 cm. The release tube is connected through a stopcock (1) to a 40-cm. condenser jacket (*D*). This is filled with 4-mesh anhydrous calcium chloride held in place by plugs of glass wool at the ends. A second condenser jacket (*E*) is filled about half-way with 4-mesh soda lime, then a 4- to 6-in. layer of anhydrous calcium chloride, and the remainder of the tube is packed with glass wool. The ends of the condensers are closed with rubber stoppers. Part *F* is a flowmeter, the U-tube of which should be about 20 cm. long. The bore of the capillary should be about 0.5 mm. in diameter. The flowmeter tube is filled about half full

with Hyvac pump oil. Part *G* is a condenser jacket (40 cm.) loosely packed with glass wool.

All parts up to the ozonizer may be connected with heavy rubber tubing. It is desirable to place this purification train

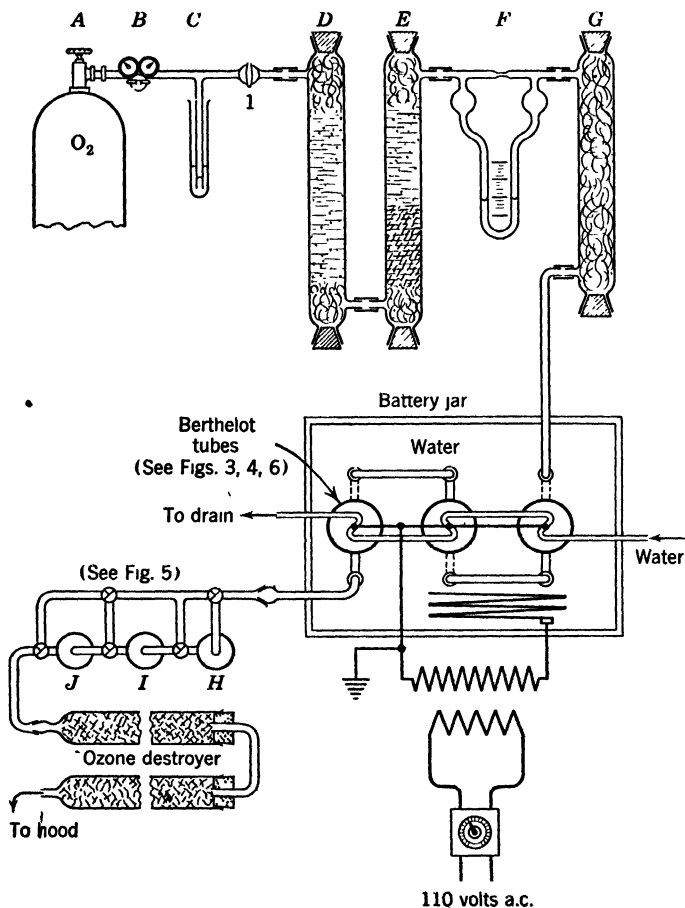


FIG. 2.

several feet from the ozonizer proper in order to prolong the life of the rubber connectors (Note 1). The sizes of parts *C* through *G* are not critical. After this part of the apparatus has been assembled, a very rapid stream of oxygen should be passed through it for 30 minutes in order to blow out all dust particles.

B. *Ozonizer*. The conversion of oxygen to ozone is accomplished by means of three Berthelot tubes constructed of soft lime glass (Note 2) with the dimensions shown in Fig. 3. It is important that the glass be thoroughly cleaned and that the

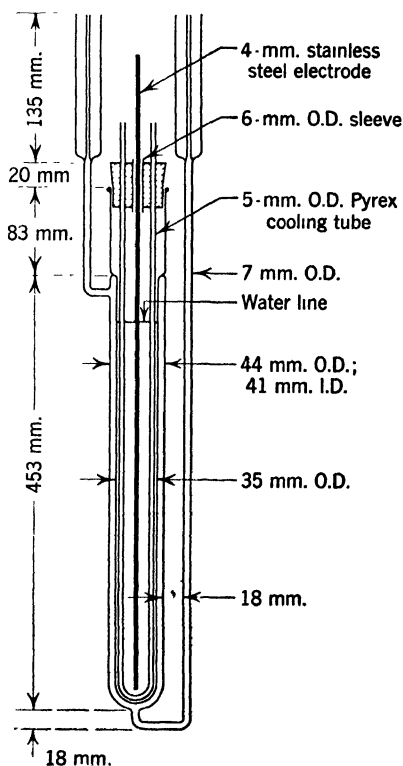


FIG. 3

annular space through which the gases pass be as uniform as possible. Each tube has a cooling coil (Note 3) consisting of a long U-shaped piece of 6-mm. Pyrex glass tubing which fits into the innermost space of the Berthelot tube and reaches nearly to the bottom. The top of the Berthelot tube is closed by a cork with three holes, two for the cooling tubes and one for the inner electrode. The last is a stainless steel rod about 2 to 4 mm. in diameter. This electrode should extend to about 1 cm. of the

bottom of the inner tube. The Berthelot tubes (Fig. 3) are connected by means of mercury-cup seals as shown in Fig. 4 (Note 4). The third Berthelot tube is connected to the reaction vessels by means of either mercury-cup seals or ground-glass joints. No rubber connectors can be used for gases containing ozone.

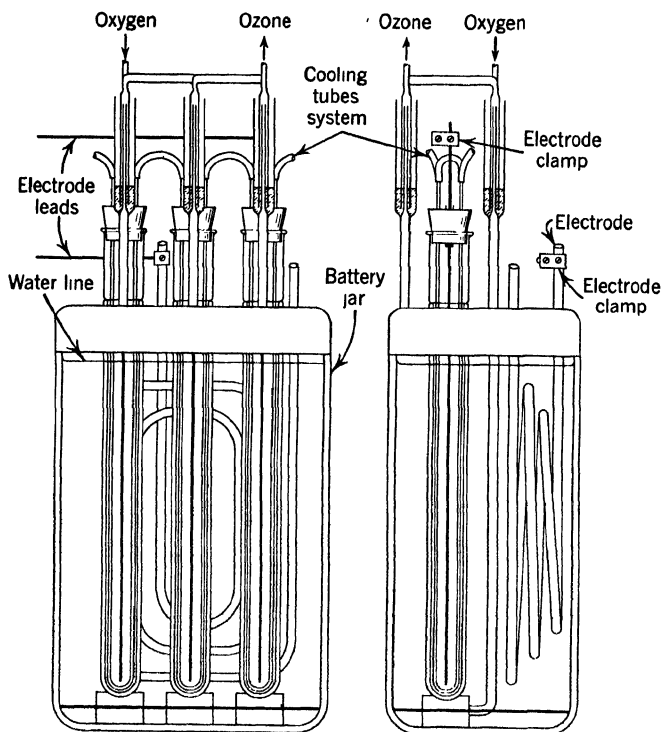


FIG. 4.

The three Berthelot tubes are mounted vertically in a large battery jar about 13 in. by 9 in. by 18 in. (Note 5). They are held in place by a wooden top (see Fig. 4) which has holes and slots cut to fit the tubes. A second wooden block with holes and slots to fit the bottom of the Berthelot tubes (Fig. 3) is placed in the bottom of the battery jar. It should be weighted with a few pieces of lead. Both the top and the bottom blocks should be soaked in hot molten paraffin wax. The holes in the top should

be directly above those in the bottom so that the Berthelot tubes will be as nearly vertical as possible to facilitate making good connections (Note 6). However, a slight slant of the tubes does not affect the operation of the ozonizer.

C. Electrical equipment. A transformer operating on 110 volts alternating current having a secondary capable of producing about 8000 to 15,000 volts and a capacity of about 400 watts or more is suitable. It is important that provision be made for varying the secondary voltage. This may be done by purchasing a transformer provided with taps on the primary windings or by inserting a variable transformer in series with the primary (Note 7). During the initial test runs for calibration it is desirable to connect an ammeter in the primary circuit in order to make certain the transformer is not overloaded.

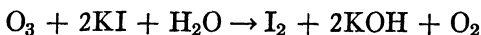
The inner electrodes of the Berthelot tubes are connected to one of the secondary terminals of the transformer. *This wire must be grounded* (Note 8); otherwise the cooling tube inside the Berthelot tube will act as a conductor to the water line and the laboratory water line would be charged. The other wire from the secondary is connected to the electrode in the battery jar. This outer electrode consists of a grid of stainless steel wire (No. 8 or 10 B. and S. gauge). Connecting the inner electrode to the ground results in a charge on the battery jar. *Precautions* must be taken so that the jar is not touched while the current is passing. Also the battery jar must be kept away from any of the plumbing so that it will not be grounded. It is best to arrange a wooden shield so that the operator cannot come in contact with any of the high-voltage connections of the secondary.

D. Ozone absorption assembly. One useful combination of reaction flasks is shown in Fig. 5. It is best that the parts be connected by ground-glass joints. Tube *II* is the main reaction flask (Note 9), *I* is a condensing tube surrounded by acetone and Dry Ice to trap any volatile compounds, and *J* is an auxiliary analyzing tube for determining the amount of ozone not absorbed by the compound in tube *H*. The tubes should be assembled and clamped high enough above the desk for cooling baths to be placed around tubes *H* and *I* in order that ozonizations

may be carried out at temperatures below that of the surroundings.

E. *Ozone destroyer.* Ozone is a powerful irritant. The maximum possible working concentration has been reported to be 0.15 to 1.0 part per million of air.¹ It is necessary to destroy any excess ozone and to see that the exit tube from the above absorption assembly is connected to a good hood. It is safer to incorporate an ozone destroyer in the set-up. One such destroyer consists of two tall towers (30 in.) filled with broken glass moistened with 5% aqueous sodium hydroxide and connected in series (Note 10). The room in which an ozonizer is used should be well ventilated.

F. *Analysis for ozone.* The analysis is made by passing a definite amount of oxygen through the ozonizer at a selected secondary voltage and then through a neutral 5% solution of potassium iodide. Iodine is liberated,



and the resulting solution is acidified with 10% sulfuric acid (about 15 ml.) and titrated with a previously standardized 0.5 *N* sodium thiosulfate solution using soluble starch as the indicator.

G. *Procedure and calibration of apparatus.* For satisfactory use of an ozonizer it is desirable to obtain data relating rate of flow and secondary voltage with the amount of ozone produced.

A wet-type gas meter (Note 11) is connected to the tube *J* as indicated in Fig. 5. Enough 5% potassium iodide solution (about 70 ml.) is added to absorption tubes *H* and *J* to fill them to a depth of about one-third to one-half their height, and the tubes are marked at this level (Note 12). The reducing valve of the oxygen tank is opened far enough to show a pressure of 3–4 lb. per sq. in.; stopcocks 2, 3, 4, 5, and 6 are turned so as to by-pass *H*, *I*, and *J* and direct the gases through the ozone destroyer. Stopcock 1 is opened far enough to give a flowmeter reading of about 2 to 3 mm.; the transformer is turned on and adjusted to a definite voltage (Note 13). After the apparatus has been swept out for 5 minutes, the stopcocks are turned so as to pass the ozonized oxygen successively through tubes *H*, *I*, *J*, and the gas

meter. The ozonized oxygen is passed through the potassium iodide solution for 5 minutes (stopwatch), and notes are made of the exact flowmeter reading and the volume of gas passing through the wet meter. At the end of 5 minutes the stopcocks are turned so as to by-pass tubes *H*, *I*, *J*, and the gas meter, and

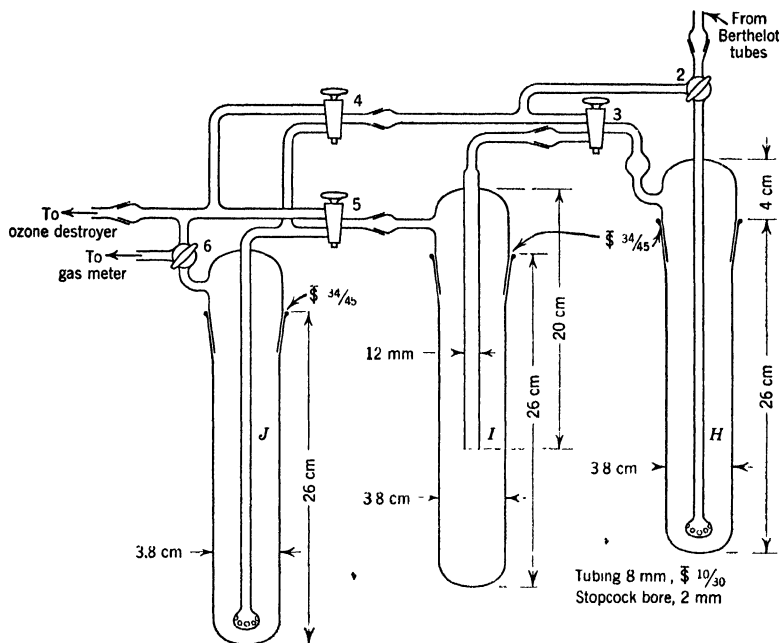


FIG. 5.

the ozonized oxygen stream is directed through the ozone destroyer. (Caution: do not pass the ozone through the wet gas meter.) The solutions in *H* and *J* are then combined, acidified, and titrated as described in paragraph F above. Practically all the ozone is absorbed in tube *H*. The second tube *J* is to prevent any damage to the wet gas meter.

The procedure is then repeated, the secondary voltage being kept constant but the rate of flow of oxygen being increased so that the flowmeter readings are about 5 mm. and 10 mm. The voltage is then changed so that the general range of 7000 to 12,000 volts in steps of about 1000 volts is obtained (Note 13). De-

terminations of ozone produced are made for each voltage and each rate of flow. These data may be plotted on coordinate paper in order to determine the performance of the ozonizer. A portion of such data is summarized in Table I, which represents the results from two different ozonizers constructed by different workers in different laboratories.

TABLE I

VARIATION IN PERCENTAGE (BY VOLUME) OF OZONE (FROM OXYGEN) WITH RATE OF FLOW AND SECONDARY VOLTAGE

Flowmeter Reading mm.	Rate of Flow l./hr.	Secondary Voltage					
		7000	8000	9000	10,000	11,000	12,000
Ozonizer 1							
2.0	5.6	1.3%	3.1%	4.5%	6.0%
6.0	10.6	0.9	2.1	4.2	5.6
12.0	15.4	0.5	1.7	3.6	4.9
Ozonizer 2							
2.0	5.7	6.7%	7.0%	7.1%	7.3%	7.2%	7.1%
5.0	9.8	6.0	6.5	6.7	7.2	6.9	6.8
10.0	14.4	5.5	6.2	6.5	6.7	6.8	6.9

For practical use in ozonolysis of compounds it is convenient to recalculate these data to show the time required to produce 0.1 mole of ozone at a specified rate of flow and voltage. This is illustrated by Table II.

TABLE II

HOURS REQUIRED TO PRODUCE 0.1 MOLE OZONE FROM OXYGEN

Flowmeter mm.	Rate of Flow l./hr.	Secondary Voltage					
		7000	8000	9000	10,000	11,000	12,000
		hr.	hr.	hr.	hr.	hr.	hr.
2.0	5.7	5.97	5.55	5.55	5.48	5.48	5.48
5.0	9.8	3.60	3.55	3.42	3.32	3.33	3.33
10.0	14.4	2.90	2.57	2.43	2.32	2.29	2.26

All ozonizers have individual characteristics since it is difficult if not impossible to build two absolutely identical ozonizers. Variations in the composition of the glass and the annular space

in the Berthelot tubes cause considerable changes in the amount of ozone produced, as shown by Table I. Hence the performances indicated by the data in Table I would be duplicated only under very fortuitous circumstances. The production of ozone from the same ozonizer may vary from time to time; hence it is desirable to check the percentage of ozone occasionally. If the production of ozone drops markedly, the Berthelot tubes should be carefully cleaned with hot nitric acid, thoroughly rinsed, and dried. Higher percentages of ozone may be obtained by having more Berthelot tubes. With six tubes, concentrations of 9% to 11% may be obtained.

H. *Ozonization of organic compounds.* The ozonization of each unsaturated organic compound is more or less an individual problem, but some general comments may be made. *Organic ozonides are highly explosive*, and hence it is safest to carry out the ozonization in a solvent which dissolves both the original compound and the ozonide. *In all cases, a shatterproof screen of laminated safety glass should be placed between the operator and the tubes H, I, and J.* A second screen should be placed back of the tubes to protect other pieces of the apparatus.

The general procedure consists in dissolving a weighed amount of the compound in a suitable solvent such as 'glacial acetic acid, methyl chloride, ethyl chloride, or carbon tetrachloride. The solution is placed in tube *H* and such an amount is used that the same hydrostatic head is obtained as when the 5% potassium iodide solution was used in both tubes *H* and *J*. Usually both tubes *H* and *I* are surrounded by cooling baths. The ozonizer is started and the gases by-passed through the destroyer for about 5 minutes while the apparatus is attaining equilibrium. The ozonized oxygen is then passed through the solution of the compound for the calculated time. Since all organic compounds do not absorb ozone rapidly enough for a quantitative absorption it is frequently necessary to run the ozonization longer. The presence of unsaturation may often be detected by testing a small portion of the reaction mixture with a dilute solution of bromine in carbon tetrachloride. The ozonization is continued until the test with the bromine solution is negative.

It is also possible to place a solution of the compound in tube *H* to the proper height and use a 5% potassium iodide solution in tube *J*. At the end of the calculated time the contents of tube *J* are titrated in order to determine the amount of ozone that failed to react with the compound. From these data the additional time necessary to complete the ozonization is calculated and the apparatus operated accordingly (Notes 14 and 15).

The procedures for the decomposition of the ozonide and separation of the reaction products will vary according to the nature of the compounds and must be designed and selected accordingly.

Selective ozonization of compounds containing different types of unsaturated linkages is possible by choosing a proper concentration of ozone and by stopping the ozonization at the right time. It is for this reason that the calibration described above is carried out, since for certain ozonizations it is important to have the correct concentration for best results.

I. Use of air in place of oxygen. When air is the source of oxygen the exit gases from the Berthelot tubes contain lower percentages of ozone than when pure oxygen is used. The gases also contain small amounts of nitric anhydride,² the presence of which may cause some side reactions to occur. However, a considerable number of compounds may be satisfactorily ozonized with air as the source of oxygen. The above apparatus will operate satisfactorily with compressed air. It is essential to bubble the compressed air through three 5-l. flasks half filled with concentrated sulfuric acid before passing the air into the purification train *B, C, D, E, F, G*. Some data on the production of ozone from air at a secondary potential of 10,000 volts are given in Table III.

TABLE III

PRODUCTION OF OZONE FROM AIR AT SECONDARY VOLTAGE OF 10,000

	Rate of Flow	
	15.3 l./hr.	21.8 l./hr.
Ozone, % by volume	3.0	2.9
Hours for production of 0.1 mole ozone	4.8	3.4
N ₂ O ₅ , % by volume	0.13	0.08
Moles HNO ₃ formed per 0.1 mole ozone	0.009	0.006

At higher secondary voltages the percentage of nitrogen pentoxide rises. A decrease in the rate of flow also increases the amount of nitrogen pentoxide. It is obvious from the data in Table III that the amounts of nitrogen pentoxide are very small and need to be considered only when examining a reaction mixture for small amounts of by-products or when the presence of this oxide of nitrogen would act as a catalyst for the oxidation of the organic compounds by oxygen or ozone.

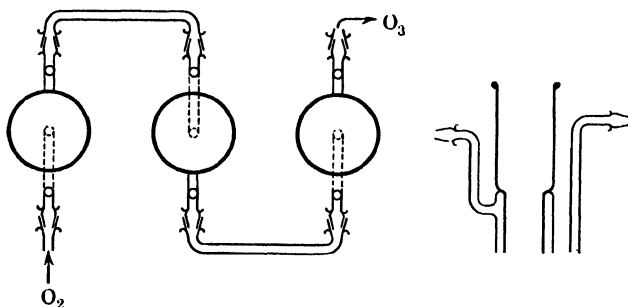


FIG. 6.

2. Notes

1. If necessary, the rubber connecting tubes in the purification train may be protected by painting them with molten paraffin wax.

2. Berthelot tubes constructed of Pyrex either fail to produce ozone or give a low yield.³ However, Henne and Perilstein⁴ have recently described a satisfactory ozonizer constructed of Pyrex glass.

3. It is necessary to cool the water inside the Berthelot tubes since the temperature of the small volume of water in the inner tube reaches 40° or higher a short time after the current is turned on, with consequent reduction in the amount of ozone produced. It is usually not necessary to cool the large volume of water in the battery jar.

4. The mercury-cup seals may be replaced by ground-glass joints lubricated with a *very small* amount of 85% phosphoric acid. If ground-glass connections are used the inlet and outlet

tubes should be bent to facilitate union. Figure 6 shows top and side views of such Berthelot tubes. The holes in the wooden supports should be large enough to permit the tubes to fit loosely.

5. Any large commercial laboratory battery jar is suitable. The Exide types F-9 or F-11 are satisfactory.

6. The dimensions of these wooden supports will be determined by the battery jar. The position of the holes and slots should be arranged so that the tubes may be spaced at convenient distances as shown in Fig. 4.

7. The submitters used a transformer purchased from the Franklin Transformer Company, Minneapolis, Minnesota, for \$25-30. It was provided with taps so that secondary voltages of 5500, 6600, 7700, 8800, 9900, and 11,000 could be obtained. These transformers do not always deliver the rated voltage and hence should be calibrated by actual measurement. The checkers used a luminous tube transformer obtained from the Jefferson Electric Company, Bellwood, Illinois, Cat. No. 721-411. Cap. 825 VA. Primary 115 V.A.C. 60 cycles. Secondary 15,000 V. 60 M.A. Price \$19.60. The variable transformer used to regulate the voltage should be rated at 7.5 amperes and may be a Varitran, Adjustavolt, or Variac.

8. It may make a difference which side of the transformer is grounded, depending on the construction of the transformer; the maker of the transformer should be queried on this point.

9. The reaction flask *H* can be made of different sizes depending on the amount of solution being ozonized. The dimensions of the parts in Fig. 5 are not critical; any tubes and stopcocks of convenient size are suitable.

10. Many reagents act as contact catalysts for the destruction of ozone; a study of some of them has been made.⁵

11. A wet gas meter such as No. S-39465, E. H. Sargent and Company, is satisfactory. This meter need not be a permanent part of the apparatus. It is used only to calibrate the flowmeter.

12. In order that the flowmeter may be used during an ozonization when tube *J* is empty it is necessary to mark the heights of liquid on both tubes. The same liquid head (height \times density) must be present in the absorption tubes during calibra-

tion and ozonization. For very accurate work a pressure regulator should be incorporated in the oxygen train and a gas meter made part of the set-up. For ordinary preparative work, however, these are not necessary.

13. If a transformer with taps is used the voltage chosen is determined by each tap. With a luminous tube transformer and Variac, a voltmeter is connected across the primary of the transformer. Since these transformers have a fixed ratio of primary to secondary windings, the secondary voltage will be nearly proportional to the impressed primary voltage. Thus a transformer designed to deliver 15,000 volts with a primary voltage of 115 volts will deliver approximately 12,000 volts when the primary voltage is $\frac{4}{5}$ of 115 or 92 volts.

14. It is evident that for ordinary preparative work the careful calibration given in section G is not essential. It is only necessary to adjust the voltage of the transformer to about 10,000 to 11,000 volts and turn on the flow of oxygen to as rapid a rate as the absorption tubes will handle when surrounded by cooling baths. The amount of ozone produced in 5 minutes at the observed flowmeter reading is determined as in section F. By operating the ozonizer at this rate of flow and voltage the ozonization of organic compounds can be carried out.

15. The ozonizer may be operated at higher rates of flow of oxygen than shown in Tables I and II, provided that the organic compound reacts with ozone at a reasonably rapid rate. Some data on high rates of flow are given in Table IV.

TABLE IV

PRODUCTION OF OZONE FROM OXYGEN AT HIGH RATES OF FLOW AND SECONDARY VOLTAGE OF 10,000

Rate l./hr.	% Ozone (by volume)	Hours to Produce 0.1 Mole Ozone
27	4.7	1.76
32	4.5	1.55
45	4.1	1.23

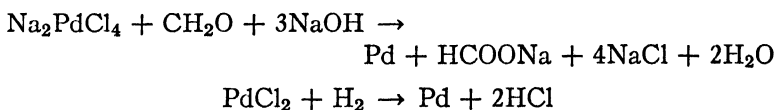
3. Methods of Preparation

Ozone for laboratory use has always been prepared by the action of the silent electric discharge upon a stream of air or oxygen. Although dielectrics other than glass are used in commercial ozonizers, they do not give a percentage of ozone high enough for laboratory use, and practically all laboratory ozonizers employ the Berthelot tube and are modeled after the one originally constructed by Harries.⁶ Good ozonizers of this type have been described by Briner, Patry, and de Luserna,⁷ and by Church, Whitmore, and McGrew.⁸ The ozonizer described above is a modification of the one described by Smith,⁹ as improved by Henne,¹⁰ and by Smith and Ulliot³ and Greenwood.¹¹ Henne and Perilstein⁴ described a modification of their ozonizer in which the inner electrode is a tube filled with mercury; the outer electrode is water-cooled.

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PALLADIUM CATALYSTS



Submitted by RALPH MOZINGO.

Checked by HOMER ADKINS and JAMES E. CARNAHAN.

1. Procedures (Note 1)

A. *Palladium on barium sulfate catalyst* (5% Pd). A solution (Note 2) of 8.2 g. of palladium chloride (0.046 mole) in 20 ml. (0.24 mole) of concentrated hydrochloric acid and 50 ml. of water is prepared. To a rapidly stirred, hot (80°) solution of 126.2 g. (0.4 mole) of reagent barium hydroxide octahydrate in 1.2 l. of distilled water contained in a 4-l. beaker (Notes 3 and 4) is added all at once 120 ml. (0.36 mole) of 6 *N* sulfuric acid. More 6 *N* sulfuric acid is added to make the suspension just acid to litmus (Note 5). To this hot barium sulfate suspension (Note 6) is added the palladium solution and 8 ml. (0.1 mole) of 37% formaldehyde solution. The suspension is then made slightly alkaline to litmus with 30% sodium hydroxide solution, constant stirring being maintained. The suspension is stirred 5 minutes longer and then the catalyst is allowed to settle (Note 7). The clear supernatant liquid is decanted and replaced by water, and the catalyst is resuspended. The catalyst is washed by decantation eight to ten times. After the final decantation, the catalyst is collected on a 90-mm. medium-porosity sintered-glass funnel (Note 8). Most of the water is removed from the cake, but not enough to cause the cake to break or channel. The filter cake is washed with 250 ml. of water in five portions, the last being removed as completely as possible by filtration. The funnel and its contents are then placed in an oven at 80° until the catalyst is dry. The catalyst (93–98 g.) is powdered and stored in a tightly closed bottle (Note 9).

B. *Palladium on carbon catalyst (5% Pd)*. A suspension of 93 g. of nitric acid-washed Darco G-60 (Note 10) in 1.2 l. of water contained in a 4-l. beaker (Notes 3 and 4) is heated to 80°. To this is added a solution of 8.2 g. (0.046 mole) of palladium chloride in 20 ml. (0.24 mole) of concentrated hydrochloric acid and 50 ml. of water (Note 2). Eight milliliters (0.1 mole) of 37% formaldehyde solution is added. The suspension is made slightly alkaline to litmus with 30% sodium hydroxide solution, constant stirring being maintained. The suspension is stirred 5 minutes longer. The catalyst is collected on a filter and washed ten times with 250-ml. portions of water. After removal of as much water as possible by filtration, the filter cake is dried (Note 11), first in air at room temperature, and then over potassium hydroxide in a desiccator. The dry catalyst (93–98 g.) is stored in a tightly closed bottle.

C. *Palladium chloride on carbon (5% Pd)*. A solution of 8.2 g. (0.046 mole) of palladium chloride in 20 ml. (0.24 mole) of concentrated hydrochloric acid and 50 ml. of water is prepared (Note 2). The solution is diluted with 140 ml. of water and poured over 92 g. of nitric acid-washed Darco G-60 (Note 10) in an 8-in. evaporating dish (Note 3). After the palladium chloride solution has been thoroughly mixed with the carbon, the whole mixture is dried, first on a steam bath and then in an oven at 100°, with occasional mixing until completely dry. The mass (98–100 g.) is powdered and stored in a closed bottle.

The required quantity of palladium chloride on carbon is transferred to a hydrogenation bottle and reduced with hydrogen in the solvent to be used for the hydrogenation (Notes 12 and 13). When no more hydrogen is absorbed by the catalyst, it is collected (Note 14) on a sintered-glass funnel and washed with more of the solvent to remove the hydrogen chloride, and then returned to the reduction bottle, the last being washed in with the solvent. The material to be hydrogenated is then added and the hydrogenation is completed in the usual way.

D. *Palladium on carbon catalyst (10% Pd)*. A solution of 8.33 g. of palladium chloride in 5.5 ml. of concentrated hydrochloric acid and 40 ml. of water is prepared by heating the mixture on a

steam bath (Notes 2 and 15). The resulting solution is poured into a solution of 135 g. of sodium acetate trihydrate in 500 ml. of water contained in a 1-l. reduction bottle (Note 16). Forty-five grams of Norite (Note 10) is added, and the mixture is hydrogenated until absorption ceases after 1 to 2 hours. The catalyst is collected on a Büchner funnel and washed with 2 l. of water in five portions. The filter cake, after removal of most of the water, is dried in air and then in a desiccator over calcium chloride (Note 11). The catalyst (48–50 g.) is stored, after being powdered, in a tightly closed bottle.

2. Notes

1. The four procedures given for the preparation of palladium catalysts differ in that in A the support is barium sulfate or barium carbonate whereas in the others the support is carbon. In procedures A and B, alkaline formaldehyde is the reducing agent; in C and D, hydrogen is used. The catalysts A, B, and D are prepared and stored until required with the palladium in the reduced form ready for use. In C,¹ the palladium salt is reduced to the metal as needed, so that there is no loss of activity during storage. Catalyst A is similar to that usually recommended for Rosenmund reductions; D is essentially that developed by Hartung² and extensively used by Cope³ and others. Catalyst D carries twice as much palladium per unit weight as the others.

Catalysts reduced with formaldehyde carry no adsorbed hydrogen and are less pyrophoric. Barium carbonate as a support may sometimes be advantageous in that the neutrality of the hydrogenation mixture may be maintained. Barium sulfate or barium carbonate may be a better support than carbon, which may, in some instances, so strongly adsorb the derived product that recovery is difficult or incomplete. Palladium may be more completely and easily recovered from a spent catalyst where carbon rather than barium sulfate is the support. In general, the submitter prefers a catalyst prepared according to procedure C.

2. Since palladium chloride dissolves rather slowly in aqueous acid, the mixture is heated on a steam bath for about 2 hours, or until solution is complete. If the dihydrate of palladium chloride is used the quantity should be increased to 9.9–10.0 g.

3. The entire preparation is carried out with all-glass or porcelain equipment in order to prevent contamination with iron or other metals.

4. The catalyst may be prepared in ten times the amount given here, with a 20-l. battery jar in place of the beaker.

5. The rapid addition of sulfuric acid is made to give finely divided barium sulfate.

6. An equal weight of precipitated barium carbonate (93 g.) may be substituted for the barium hydroxide and sulfuric acid to give a palladium on barium carbonate catalyst. The amount of hydrochloric acid should then be reduced to 8.2 ml.

7. After 5 minutes, the solution is colorless and free of palladium chloride.

8. A Büchner funnel may be used, but filtration through paper is very slow. The washing process may be carried out by centrifugation instead of filtration.

9. The palladium may be conveniently separated from the barium sulfate by solution in aqua regia. The used catalyst is collected from the reaction mixture on a sintered-glass funnel. The organic material is removed with suitable solvents, and the solvents are replaced by water. The palladium is dissolved in aqua regia and is washed out with dilute hydrochloric acid, the solutions being collected for recovery of the metal. For recovery of the palladium from carbon, the mass is ignited and the ash is extracted with aqua regia for several hours. The palladium solution is filtered, and any residue is reignited and then treated with alkaline formaldehyde solution to reduce any oxides of palladium which may have been formed, and which are only slowly soluble in aqua regia. The solids are collected on a filter, and the palladium is extracted with aqua regia.

10. Norite, Darco, or other carbons, may be used. The carbon is heated on a steam bath with 10% nitric acid for 2 to

3 hours, washed free of acid with water, and dried at 100–110° before use.

11. The palladium on carbon catalysts should be dried at room temperature or the carbon may ignite. These catalysts are first dried in air and then over potassium hydroxide (or calcium chloride) in a desiccator.

12. The solvent is conveniently that in which the hydrogenation is to be done. During the reduction of the palladium chloride, a neutral solvent is to be preferred; any acid or alkali needed for the hydrogenation is added after reduction of the catalyst.

13. The presence of hydrogen chloride during the hydrogenation of many organic compounds is desirable or without effect, so that the washing operations may be omitted in such cases. Thus, the palladium chloride on carbon may be used in the same manner as the prereduced catalysts, i.e., simply added before reduction to the solvent and the hydrogen acceptor.

14. The catalyst should be kept wet with the solvent during the washing process, as it is pyrophoric.

15. The resulting solution is approximately equivalent to 50 ml. of the commercial palladium chloride solution (p. 32) suggested by Hartung and Cope.³

16. The checkers reduced the palladium chloride, in three batches, in a 500-ml. bottle. The bottle was not shaken, but the contents were rapidly stirred under a pressure of 1.1 atmospheres of hydrogen. The reduction of each batch required about 5 hours.

3. Methods of Preparation

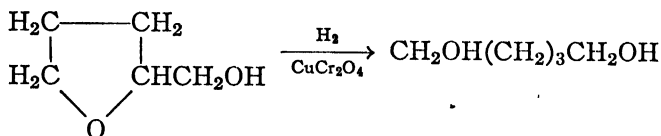
Palladium catalysts have been prepared by fusion of palladium chloride in sodium nitrate to give palladium oxide;^{4, 5} by reduction of palladium salts by alkaline formaldehyde^{6, 7, 8} or sodium formate,⁹ by hydrazine¹⁰ and by the reduction of palladium salts with hydrogen.¹¹ The metal has been prepared in the form of palladium black,^{6, 9} and in colloidal form in water containing a protective material,¹⁰ as well as upon supports. The supports commonly used are asbestos,¹² barium carbonate,¹³

barium sulfate,^{1, 7, 8, 14} calcium carbonate,¹⁵ carbon,^{1, 11, 14, 16} kieselguhr,^{14, 16} silica-gel,¹⁷ and strontium carbonate.¹⁸ The catalysts described here are prepared by modifications of the methods of Schmidt,⁸ Rosenmund and Langer,¹⁴ Mannich and Thiele,¹¹ and Hartung.^{2, 3}

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- ¹⁸ Martin and Robinson, *J. Chem. Soc.*, **1943**, 491.

1,5-PENTANDIOL



Submitted by DANIEL KAUFMAN and WILKINS REEVE.
 Checked by HOMER ADKINS and HARRY BILLICA.

1. Procedure

Five hundred and ten grams (5 moles) of pure tetrahydrofurfuryl alcohol (Note 1) and 50 g. of copper chromite (Note 2) are placed in a hydrogenation bomb having a void of 1400 ml. (Note 3). The bomb, in a suitable rocker assembly, is filled with hydrogen to a pressure of 3300 to 3500 lb. per sq. in. (Note 4). The bomb is rocked and heated. *The pressure must not at any time be allowed to go much above 6000 lb. per sq. in.* If the pressure rises higher than 6200 pounds, the heating of the bomb should be stopped (Note 5). In a typical run, the pressure reaches a maximum of about 6100 lb. at 255° after 2 hours. The pressure then slowly falls to about 4400 lb. during another hour, as the temperature rises to a little over 300°. During the ensuing 6 hours, the pressure falls to about 3000 pounds while the temperature is held at 300–310°.

The bomb is allowed to cool to room temperature, where the pressure should be 1000–1100 lb. The contents of the bomb are poured into a beaker, and the bomb is rinsed twice with 100-ml. portions of acetone. The catalyst is removed by centrifuging, and the reaction mixture is distilled through a fractionating column (Note 6). A fraction boiling in the range 60–140°, containing α -methyltetrahydrofuran, water, and *n*-amyl alcohol, is distilled at atmospheric pressure (Note 7). Tetrahydrofurfuryl alcohol (80–110 g.) is recovered, boiling at 65–70°/10 mm.; the 1,5-pentandiol boiling at 118–120°/6 mm. is obtained in amounts

varying from 200 g. to 244 g. The yield is 40–47% of the theoretical, without allowance being made for the recovered tetrahydrofurfuryl alcohol. The residue of products boiling above the glycol amounts to 25–35 g.

2. Notes

1. The tetrahydrofurfuryl alcohol available from the Quaker Oats Company, or the Practical grade from the Eastman Kodak Company, has been used. If the material available does not hydrogenate satisfactorily, it may be purified by hydrogenation over Raney nickel at 150°/100–200 atmospheres pressure. A sample of good quality boils at 177–178°/740 mm. and does not become dark-colored when a few milliliters are shaken with 1 drop of concentrated sulfuric acid at room temperature.

2. The catalyst is prepared as described in Note 11 for the preparation of copper chromite.¹

3. The hydrogenation bomb supplied under catalog No. 406–21, by the American Instrument Company, Silver Spring, Maryland, is satisfactory. The internal volume of the empty bomb should be at least 2.7 times that of the volume of tetrahydrofurfuryl alcohol added, as otherwise not enough hydrogen can be added for the completion of the reaction, without the use of excessively high pressures. The submitters maintained the pressure above 5500 lb. per sq. in. by intermittently adding hydrogen.

4. Temperatures higher than about 300° and pressures higher than 6000 lb. per sq. in. should not be used in the vessels and with the gauges ordinarily supplied for “high-pressure” hydrogenations. *Only clean equipment, in first-class condition, and under careful control, can be used safely and successfully in carrying out reactions under the conditions described.*

5. If hydrogenolysis does not occur, the pressure would be about 7000 lb. when a temperature of 300° is reached. If the pressure rises above 6200, starting with 3500 lb. at room temperature, it is evident that the quality of the catalyst or the alcohol is not satisfactory. Further attempts to prepare the glycol should be made with alcohol and catalyst of better quality,

or starting with a pressure sufficiently low (3000 lb.) so that a safe operating pressure will not be exceeded.

6. A Vigreux-type column 60 cm. in length and 2 cm. in outside diameter was used for the fractionation. The submitters state that they have also used a column of similar dimensions, packed with glass helices, for a fractionation at atmospheric pressure. They recommended the Vigreux column under reduced pressure, as used by the checkers.

7. When acetone was not used for washing out the bomb, a fraction weighing 70–75 g. was obtained by the submitters. After drying over anhydrous potassium carbonate, they obtained, by fractional distillation, 3–6 g. of α -methyltetrahydrofuran, b.p. 80–81°, and 23–28 g. of *n*-amyl alcohol, b.p. 137–138°. The alcohol obtained was pure, and neither secondary amyl nor butyl alcohols could be detected.

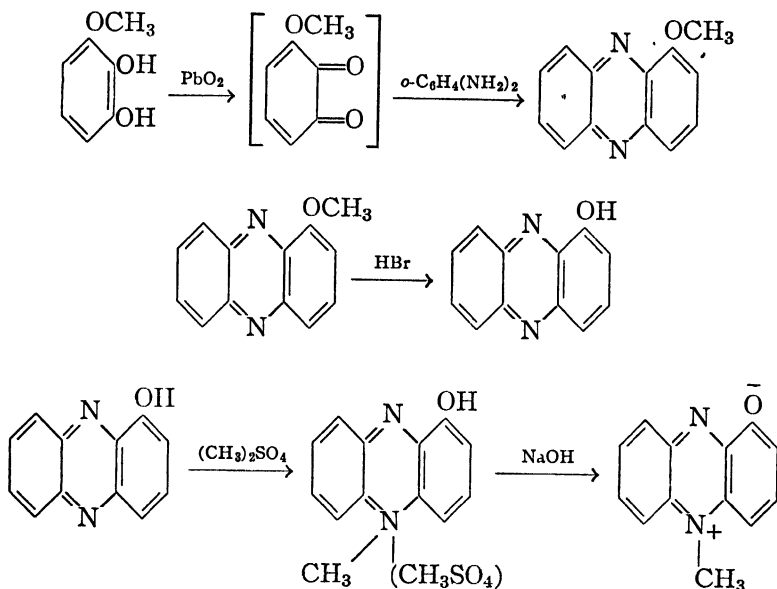
3. Methods of Preparation

1,5-Pentandiol has been prepared by the reduction of methyl glutarate^{2,3} and by the reduction of epoxy-1,5-pentanol-5.⁴ It has also been prepared from pentamethylene bromide by conversion to the diacetate followed by hydrolysis to the glycol.⁵ The procedure described is a modification of that of Connor and Adkins.⁶

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PYOCYANINE



Submitted by ALEXANDER R. SURREY.

Checked by LEE IRVIN SMITH and CHIEN-PEN LO.

1. Procedure

A. *α-Methoxyphenazine (condensation)*. Two hundred grams (0.42 mole) of powdered lead dioxide (Note 1) is added to a solution of 10 g. (0.07 mole) of pyrogallol monomethyl ether (p. 90) in 3 l. of dry benzene in a 1-gal. narrow-necked acid bottle. The bottle and contents are placed in a shaking machine and shaken for 10–20 minutes (Note 2). The reddish brown solid is filtered through an 11-cm. Büchner funnel, and the filter cake is washed once with 400 ml. of benzene. To this filtrate there is added, immediately and with mechanical stirring, a solution of 6 g. (0.06 mole) of *o*-phenylenediamine (Note 3) in a mixture of 80 ml. of glacial acetic acid and 200 ml. of benzene. The solu-

tion, which becomes dark brown, is allowed to stand at room temperature for 1.5 hours; it is then divided into two portions and each portion is washed, in a 3-l. separatory funnel, three times with water, twice with 5% sodium hydroxide solution, and finally twice with water, 100-ml. portions being taken each time. Each of the benzene solutions is shaken with 50 g. of anhydrous sodium carbonate and 5 g. of Norite and filtered through an 11-cm. Büchner funnel. Each filtrate is stirred with 50–60 g. of activated alumina (Note 4) until a filtered sample shows a light yellow color. The alumina is filtered on a folded filter and washed with benzene until the washings are almost colorless. The benzene is removed from the combined filtrates by distillation under reduced pressure on a water bath at 40–50°. The residual light yellow solid (Note 5) is recrystallized by dissolving it in the least possible amount of hot pyridine, adding water to the point of incipient precipitation, and cooling. The light yellow crystals are filtered on a 7-cm. Büchner funnel, washed with water, and air dried. The yield is about 5 g. (33%) of a product that melts at 167–169° (Note 6).

B. *α-Hydroxyphenazine (demethylation)*. A solution of 4.2 g. (0.02 mole) of *α*-methoxyphenazine, from A above, in 125 ml. of 55% hydrobromic acid (Note 7) is placed in a 250-ml. round-bottomed flask fitted with a reflux condenser. The flask is immersed in an oil bath, and the solution is heated to 110–120° for 5 hours; the evolved gases are absorbed with water in a trap.¹ The reaction mixture is cooled to room temperature, diluted with about 125 ml. of water, almost neutralized with sodium hydroxide (Note 8), and extracted six times with 30- to 40-ml. portions of ether. The combined ether extracts are extracted with 25-ml. portions of 10% sodium hydroxide solution (Note 9) until no more purple sodium salt is removed from the ether. The aqueous extracts are combined, made acid to litmus with dilute acetic acid, and re-extracted four times with 50-ml. portions of ether. The combined ether extracts are dried over anhydrous sodium sulfate, and the ether is removed by distillation on a steam bath. The residue is recrystallized as follows: It is dissolved in the least possible amount of hot alcohol, water

is added to the point of incipient precipitation, then 0.5 g. of Norite is added, and the hot solution is filtered. The filtrate is cooled in ice water, and the orange solid is filtered on a 7-cm. Büchner funnel, washed with water, and dried in an oven at 100°. The yield is 2.7 g. (70%) of a product which melts at 153–155°.

C. Pyocyanine (alkylation). A solution of 2 g. (0.011 mole) of α -hydroxyphenazine in 13.4 g. (10 ml., 0.1 mole) of methyl sulfate (Note 10) is placed in a 250-ml. Erlenmeyer flask fitted with a calcium chloride drying tube and heated at 100° (oil bath) for 10 minutes. The solution is allowed to cool to room temperature, and about 75 ml. of dry ether is added. The dark brown solid is filtered on a 7-cm. Büchner funnel and washed with about 150 ml. of dry ether in several portions (Note 11).

The dry methosulfate, dissolved in about 30 ml. of water, is made alkaline with 2–3 ml. of 10% sodium hydroxide, and the solution is then extracted *exhaustively* with successive 15-ml. portions of chloroform until no more blue substance is removed from the aqueous solution (Note 12). The combined chloroform solutions are extracted three times with 20-ml. portions of 5% hydrochloric acid. The combined acid extracts are made alkaline to phenolphthalein with 10% sodium hydroxide and re-extracted *exhaustively* with 25-ml. portions of chloroform until no more blue substance is removed from the aqueous solution (Note 12). The combined chloroform solutions are dried over anhydrous sodium sulfate and decanted, and the chloroform is removed by distillation under reduced pressure. The blue crystalline residue is recrystallized by dissolving it in the least possible amount of water at 60° and then cooling the solution in an ice bath. The product is filtered on a 5-cm. Büchner funnel and dried in the dark in a vacuum desiccator over calcium chloride. The yield is 1.35 g. (58%) of dark blue needles that melt at 133° (Note 13).

2. Notes

1. Lead peroxide "analytical reagent" of low manganese content was used.

2. On a scale twelve times as large, a "Lightnin" stirrer was used for 20 minutes.

3. *o*-Phenylenediamine, m.p. 99–101°, from Eastman Kodak Company was used.

4. The amount of alumina needed depends upon the color of the benzene solution. Sufficient alumina (activated alumina, 80 mesh, from Aluminum Corporation of America) is taken so that the filtrate is only light yellow in color. On the larger scale only 100–200 g. of alumina was needed.

5. The residue, without recrystallization, is pure enough for the preparation of α -hydroxyphenazine.

6. The submitter reports yields somewhat higher (33–40%) and states that, on a larger scale, the yields are slightly better than 40%.

7. The concentration of hydrobromic acid used ranged from 50% to 55%.

8. Concentrated sodium hydroxide solution (about 100 ml. of 35%) is used at the beginning of the neutralization, and dilute sodium hydroxide solution is added towards the end. The reaction mixture should be just faintly acid to litmus.

9. If any solid sodium salt separates during the extraction, it can be redissolved by adding water.

10. The methyl sulfate should be freshly distilled under reduced pressure.

11. The yield of methosulfate is practically quantitative.

12. The solution must be extracted *exhaustively*; the checkers found that thirty such extractions were required to remove all the product. A continuous extractor might be used at this point and certainly would be necessary for large-scale runs.

13. The same percentage yield was obtained with double the amounts specified above. The pyocyanine thus obtained can be stored in a vacuum desiccator in the dark for several weeks without appreciable decomposition. It slowly decomposes on longer standing to give the yellow α -hydroxyphenazine.

3. Methods of Preparation

This series of reactions is essentially the one described by Wrede and Strack.² Pyocyanine can also be prepared by the photochemical oxidation of phenazine methosulfate.³

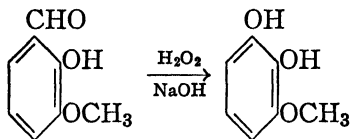
References

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³ McIlwain, *J. Chem. Soc.*, **1937**, 1708.

PYROGALLOL 1-MONOMETHYL ETHER



Submitted by ALEXANDER R. SURREY.

Checked by LEE IRVIN SMITH and CHIEN-PEN LO.

1. Procedure

The apparatus consists of a 1-l. three-necked flask fitted with a gas inlet tube extending about 3 cm. into the flask and connected to the flask through a bubbler, a thermometer extending to the bottom, a mechanical stirrer, and a reflux condenser connected at the upper end with an exit tube leading to the hood. The reaction is carried out in an atmosphere of illuminating gas (Note 1).

In the flask are placed 60.8 g. (0.4 mole) of 2-hydroxy-3-methoxybenzaldehyde (Note 2) and 200 ml. of 2*N* sodium hydroxide (0.4 mole). The mixture is stirred until almost all the solid has dissolved. The stirrer is replaced by a dropping funnel which contains 284 ml. (0.5 mole) of 6% hydrogen peroxide (Note 3). With occasional shaking, the hydrogen peroxide is added in portions of 20–25 ml. About 1 hour is required for the addition; the temperature is kept between 40° and 50°. After the addition of the first portion of hydrogen peroxide, the temperature rises to about 45° and a dark solution results. The temperature is allowed to fall to 40° before the next portion of the peroxide is added.

After all the hydrogen peroxide is added, the reaction mixture is allowed to cool to room temperature and is then saturated with sodium chloride, after which it is extracted four times with 100-ml. portions of ether. The combined extracts are dried over sodium sulfate. The ether is removed by distillation on a steam bath, and the residue is then distilled under reduced pressure. Pyrogallol monomethyl ether is collected at 136–138°/22 mm. The yield is 38–44.5 g. (68–80%) of a colorless to light yellow oil which solidifies on standing (Note 4).

2. Notes

1. Nitrogen can be used in place of illuminating gas. The gas is introduced at the rate of about 3 bubbles per second.

2. Practical 2-hydroxy-3-methoxybenzaldehyde (Eastman Kodak Company) was used in this preparation. Care should be taken when working with this material as its vapors are irritating and will cause sneezing.

3. The hydrogen peroxide solution was prepared by diluting 63 g. of a solution containing 27% hydrogen peroxide with water to 284 ml.

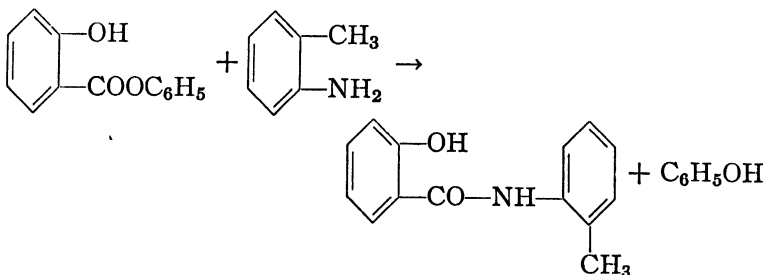
4. The procedure described is similar to that of Dakin¹ for the preparation of catechol.² The reaction has been carried out using four times the quantities specified here; the yield was 81% (C. F. H. Allen, private communication)

3. Methods of Preparation

Pyrogallol monomethyl ether has been prepared by the methylation of pyrogallol with dimethyl sulfate³ or methyl iodide;⁴ by the decarboxylation of 2,3-dihydroxy-4-methoxybenzoic acid;⁵ and by the methylation of pyrogallol carbonate with diazomethane and subsequent hydrolysis.⁶ The method described is taken from the improved procedure of Baker and Savage⁷ for the preparation of pyrogallol monomethyl ether from *o*-vanillin by oxidation with hydrogen peroxide.

References

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SALICYL-*o*-TOLUIDE(*o*-Salicylotoluide)

Submitted by C. F. H. ALLEN and J. VANALLAN.
 Checked by H. R. SNYDER and R. L. ROWLAND.

1. Procedure

In a 250-ml. flask attached to a Vigreux column 30 cm. in over-all length (Note 1), a mixture of 42.8 g. (0.2 mole) of phenyl salicylate ("Salol," m.p. 42–43°), 26.7 g. (0.25 mole) of *o*-toluidine, and 60 g. of 1,2,4-trichlorobenzene (m.p. 15–16°), is heated at the boiling point, so that the phenol formed slowly distills. The temperature rises from 183° to 187° during the first hour, and 22–23 g. of distillate is collected. Heating is continued until the temperature rises to 202° and a total of 45–46 g. of distillate has been collected (Note 2). The flask is then removed, and to it are added 3 g. of Norite and 10 ml. of trichlorobenzene. The mixture is heated to boiling and filtered hot by suction. The

filtrate is allowed to stand in the ice chest overnight. The crystalline amide is filtered by suction, slurried with 75 ml. of ligroin (b.p. 90–120°) at 35–40°, and filtered. After being dried to constant weight, the salicyl-*o*-toluide, m.p. 143–144°, amounts to 33–35 g. (73–77%) (Notes 3, 4, 5).

2. Notes

1. These are measurements of standard ground-glass equipment.

2. The checkers preferred α -methylnaphthalene (Eastman, Practical) as the diluent. When it is used in the apparatus described the phenol does not distil, so that a reaction flask fitted with an air-cooled condenser is more convenient. The reactants in 60 g. of α -methylnaphthalene are heated in an oil bath at 230° for 1.5 to 2 hours. Three grams of Norite and 20 g. more of α -methylnaphthalene are then added, and the mixture is treated as described in the Procedure. The yield and melting point of the product are identical with those described.

3. Since the pure material¹ melts at 144°, the product needs no further purification for ordinary purposes. It has a faint odor, which can be removed by recrystallization from aqueous ethanol (suitably by solution in 8–10 ml. of ethanol per gram of material and the addition of water just short of precipitation from the hot solution). The loss in recrystallization is only about 5%; the melting point is unchanged.

4. By working up the filtrate, only about 2 g. of material of poor quality can be secured.

5. Other anilides can be prepared by this procedure.

AMINE USED	M.P. OF ANILIDE	YIELD, %
Aniline	131–132°	70
2,5-Dichloroaniline	228°	89
β -Naphthylamine	188°	84
2-Aminopyridine	206°	86
1-Aminoanthraquinone	278–284°	79

When the boiling point of the amine is widely different from that of phenol, a diluent is unnecessary though it facilitates puri-

fication. In the absence of a diluent, the hot melt is poured into alcohol and recrystallized, using a decolorizing carbon; there is considerable tendency towards crystallization during the filtration from the charcoal.

Salicylanilide (m.p. 131–132°) is obtained by heating the mixture without a diluent for 3 hours at 180–200° with a short air condenser, pouring the melt into 100 ml. of alcohol and working up as above. The persistent pink color is not easily removed.

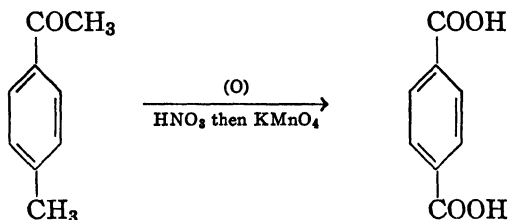
3. Methods of Preparation

Salicyl-*o*-toluide has been prepared only by the action of phosphorus oxychloride upon a mixture of salicylic acid and *o*-toluidine. The useful methods of preparation of salicylanilide are by the interaction of salicylic acid and aniline in the presence of phosphorus trichloride,^{2,3,4} by heating phenyl salicylate and aniline,⁵ and from *o*-hydroxybenzamide and bromobenzene in the presence of small amounts of sodium acetate and metallic copper.⁶ A number of these and other anilides have been described.⁷

References

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TEREPHTHALIC ACID



Submitted by C. F. KOELSCH.

Checked by C. F. H. ALLEN and J. VANALLAN.

1. Procedure

One hundred grams (0.75 mole) of *p*-methylacetophenone¹ is added to a mixture of 250 ml. (4 moles) of concentrated nitric acid (sp. gr. 1.42) and 1 l. of water in a 3-l. flask, and the mixture is refluxed in a hood for 4 hours. After the mixture has been cooled, the sticky, yellow solid is collected on a 14-cm. Büchner funnel, pressed down well, and washed with 300 ml. of cold water.

The moist solid is mixed with 1 l. of water and 35 g. of sodium hydroxide in a 3-l. three-necked flask, fitted with a mechanical stirrer and a reflux condenser, and the stirred mixture is heated almost to its boiling point. Through the momentarily opened third neck of the flask is added, in portions of about 20 g., 300 g. (1.9 moles) of potassium permanganate, at such a rate that the boiling of the stirred mixture is maintained without external heating. After the addition has been completed, the mixture is refluxed for 2 hours; if any permanganate remains it is destroyed by the addition of 25 ml. of alcohol. The mixture is then filtered through a 14-cm. Büchner funnel, and the manganese dioxide is washed by removing it from the funnel, slurring with 500 ml. of hot water (Note 1), and filtering.

The combined filtrates are heated nearly to boiling and acidified with a solution of 108 ml. of concentrated sulfuric acid (sp. gr. 1.84) in 400 ml. of water. After the mixture has been cooled to room temperature, the terephthalic acid is filtered and washed by stirring on the filter with three successive 100-ml. portions of cold water. The product is dried in an evaporating dish on a steam bath. The yield of terephthalic acid which sublimes at 300° or higher without melting is 105–109 g. (84–88%) (Notes 2 and 3).

2. Notes

1. This extraction yields 1–2 g. of the product.

2. The acid is analytically pure. There is no satisfactory solvent for the recrystallization of large amounts of terephthalic acid. Small quantities may be recrystallized from acetic acid, but the purity of a properly precipitated and washed sample is not thereby improved.

3. The high yields of ethyl ester obtainable from the product attest its purity. A mixture of 50 g. of terephthalic acid, 500 ml. of absolute ethyl alcohol, and 25 ml. of sulfuric acid was boiled for 16 hours and then distilled to half its volume and poured into dilute aqueous sodium carbonate. There was obtained 56.7 g. of diethyl terephthalate (m.p. 42–44°), and from the wash water there was recovered 4.6 g. of terephthalic acid; these materials account for 93.3% of the original substance.

3. Methods of Preparation

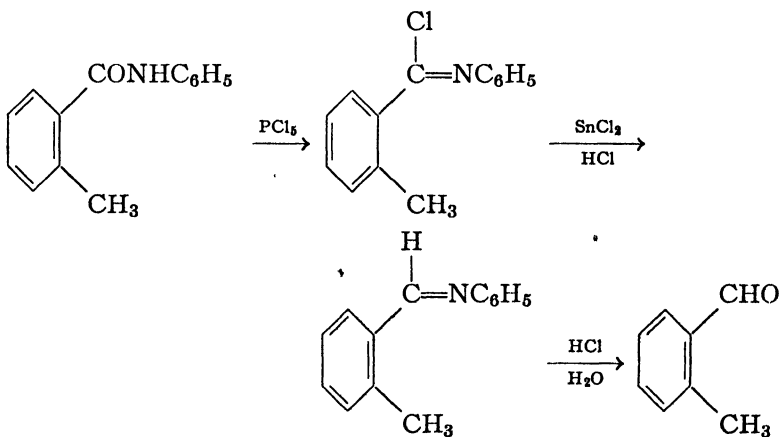
Terephthalic acid has been obtained from a great many *p*-disubstituted derivatives of benzene or cyclohexane by oxidation with permanganate, chromic acid, or nitric acid. The following routes appear to have preparative value: from *p*-toluic acid,² *p*-methylacetophenone,³ or dihydro-*p*-tolualdehyde⁴ by oxidation with permanganate; from *p*-cymene by oxidation with sodium dichromate and sulfuric acid;⁵ from *p*-dibromobenzene or from *p*-chloro- or *p*-bromobenzoic acid by heating at 250° with potassium and cuprous cyanides;⁶ and from *p*-dibromobenzene, butyllithium, and carbon dioxide.⁷

The two-stage oxidation described in the present preparation is new and appears to be more convenient than any of the procedures referred to above.

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o-TOLUALDEHYDE



Submitted by JONATHAN W. WILLIAMS, CHARLES H. WITTEN,
and JOHN A. KRYNITSKY.

Checked by W. E. BACHMANN and N. C. DENO.

1. Procedure

Thirty grams (0.14 mole) of o-toluanilide (Note 1) and 20 ml. of dry benzene are placed in a 125-ml. Claisen flask which is fitted with a condenser for distillation under reduced pressure and set in a water bath. The bath is heated to 50°, and 30 g. (0.14 mole) of phosphorus pentachloride is added to the mixture over a period of 10 minutes. The bath is then heated to 75°

and this temperature is maintained for 15 minutes. The benzene and most of the phosphorus oxytrichloride are then removed by distillation at 20 mm. from a bath at 95°. The crude *N*-phenyl-*o*-toluimidyl chloride which remains as a viscous liquid is sufficiently pure for the next step.

A mixture of 50 g. (0.26 mole) of anhydrous stannous chloride¹ and 225 ml. of dry ether is placed in a 1-l. three-necked round-bottomed flask fitted with a rubber-tube sealed stirrer,² an inlet tube reaching nearly to the bottom of the flask, and a reflux condenser (Note 2) protected by a calcium chloride drying tube. The mixture is saturated with dry hydrogen chloride³ (Note 3) with continuous stirring. Within 3 hours all the stannous chloride dissolves, forming a clear viscous lower layer. The source of hydrogen chloride is then disconnected, and the freshly prepared imidyl chloride is transferred into the mixture with the aid of 25 ml. of dry ether (Note 4). Stirring is continued for 1 hour, and then the reactants are allowed to stand at room temperature for 12 hours.

Ice (about 100 g.) and then 100 ml. of cold water are added, the mixture is stirred for 10 minutes, and then the ether is removed by distillation (Note 5). To the residue in the flask is added sufficient water to make the total volume about 300 ml. Steam distillation is then carried out until the distillate comes over clear. This process requires about 1 hour. The aldehyde is extracted from the steam distillate with three equal portions of the ether recovered above, and the ether solution is dried for several hours over anhydrous sodium sulfate.

The ether is removed by dropping the solution slowly from a separatory funnel into a 50-ml. Claisen flask fitted with a condenser for downward distillation and heated on a steam bath (Note 6), and the residual aldehyde is distilled under reduced pressure. The yield of *o*-tolualdehyde boiling at 90–93°/19 mm. is 10.5–12 g. (62–70%).

2. Notes

1. The *o*-toluanilide was prepared by the reaction of *o*-tolylmagnesium bromide with phenyl isocyanate.⁴ If the *o*-toluanilide has been recrystallized from petroleum ether, it may be necessary

to melt the light fluffy crystals (to a more compact form) in order to get all the compound into the flask.

2. A reflux condenser is not necessary if the mixture is kept ice-cold during the addition of hydrogen chloride.

3. The checkers used hydrogen chloride from one of the cylinders of hydrogen chloride now available commercially.

4. At this point considerable evolution of heat occurs. A cold water bath should be kept in readiness for application to the reaction flask.

5. The distillate, which may contain a small amount of o-tolualdehyde, is collected and used for the subsequent extraction.

6. In this step the recovered ether is collected in a dry atmosphere, and about 100 ml. of this ether is used in two portions to extract the sodium sulfate residue in order to transfer into the flask any small quantities of the aldehyde that may have been trapped by the drying agent.

3. Methods of Preparation

o-Tolualdehyde has been prepared by the oxidation of o-xylene,⁵ by the oxidation of o-xylyl chloride,⁶ by the oxidation of o-tolylcarbinol,⁷ by the reaction of o-tolylmagnesium bromide with ethyl formate,⁸ and by the reaction of o-tolylmagnesium bromide with ethoxymethylaniline.⁹ The procedure described is based on the method of Sonn and Müller¹⁰ as studied for o-tolualdehyde by King, L'Ecuyer, and Openshaw.¹¹

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- ⁹ Monier-Williams, *J. Chem. Soc.*, **89**, 275 (1906).
- ¹⁰ Sonn and Müller, *Ber.*, **52**, 1929 (1919).
- ¹¹ King, L'Ecuyer, and Openshaw, *J. Chem. Soc.*, **1936**, 352.

SUBJECT INDEX

(This cumulative index comprises material from Volumes 20 through 26 of this series; for previous volumes see Collective Volumes 1 and 2.)

Names in small capital letters refer to the titles of individual preparations. A number in ordinary bold-face type denotes the volume. A number in bold-face italics refers to a page which gives preparative directions for substances formed either as principal products or as by-products; numbers in ordinary type indicate pages on which a compound or a subject is mentioned in connection with other preparations. For example, Acetone cyanohydrin, **20**, **42**, **43**, indicates that acetone cyanohydrin is mentioned on page 42, and that directions for its preparation are given in detail on page 43, of Volume 20.

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